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## PATHOGENESIS, DIAGNOSIS AND TREATMENT OF HUMAN TOXOPLASMOSIS

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Toxoplasmosis is an infection occurring in nature. In animals it has been observed in an acute stage [1] and in a chronic latent stage.[2] In human beings the following clinical forms have been recognized, characterized chiefly by (1) congenital or neonatal meningoencephalitis, usually associated with hydrocephaly, chorioretinitis, cerebral calcifications and convulsions; (2) atypical encephalitis; (3) postencephalitic sequelae, or (4) pneumonitis associated with fever and a rash. Subclinical forms of the infection have been diagnosed from the presence of specific Toxoplasma-neutralizing antibodies in certain persons and from the delivery of toxoplasmic infants by seemingly healthy mothers.[3] I recently had the opportunity to study pathologically 5 cases of fatal congenital toxoplasmosis in 2 of which clinical diagnosis had been made and Toxoplasma isolated. The lesions produced by three strains of Toxoplasma were studied in experimental animals. In addition, about 80 patients with uveitis and more than 200 other patients were investigated clinically, serologically and by cutaneous test for evidence of past or present infection with Toxoplasma. The detailed results of these investigations are to be published elsewhere.[4] The purpose of this paper is to describe and to reinterpret the pathogenesis of the infection which will serve to facilitate diagnosis of the disease and which may form a rationale for its treatment.

### HISTORICAL INTRODUCTION

Toxoplasma gondii, the type species, was first described by Nicolle and Manceaux [5] from the Institute Pasteur in Tunis in the year 1908. The name is derived from the Greek *toxon*, meaning a bow or arc, connoting the lunate shape of the organism (fig. 1*A* and *B*). The specific name gondii is derived from the name of the type host, the gondi (Ctenodactylus gondi, Pallas, 1778), a small North African rodent, which was used as a laboratory animal at the Institute Pasteur. The organism is generally believed to be a protozoan. Reproduction is by multiple binary fission. Proliferating organisms and pseudocysts may be distinguished. In the same year (1908) Splendore [6] described the organism isolated from a rabbit in Brazil. Janků,[7] in 1923, described the first well authenticated case in a human being from Czechoslovakia. It was that of an infant with unilateral microphthalmus and bilateral chorioretinitis. In 1929, Levaditi and his co-workers [8] published an extensive experimental study of Toxoplasma isolated from rabbits. Sabin and Olitzky [9] were the first to prove the existence of the organism in North America (1937), when they encountered Toxoplasma in a guinea pig. These authors also demonstrated the development of neutralizing antibodies in the course of the disease in Rhesus monkeys. Likewise in 1937, Wolf and Cowen [10] reported the first instance of human infection with Toxoplasma in the United States. Subsequently, these authors, together with Paige, described 10 further cases in infants and children.[3a] Pinkerton and Weinman,[11] in 1940, reported the first fatal case in an adult, a Peruvian with concomitant bartonellosis. In the following year, Pinkerton and Henderson [12] published a study of 2 further fatal adult cases of toxoplasmosis, observed in the St. Louis area. Sabin,[13] in 1941, described 2 cases in children from Cincinnati characterized by encephalitic symptoms. One of these children survived. Sabin and Warren,[14] in 1942, reported successful treatment of experimental toxoplasmosis with sulfapyridine and sulfathiazole, but ineffectiveness of certain antiprotozoal drugs that were toxic in vitro.[15] The same authors [16]

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12. Pinkerton, H., and Henderson, R. G.: Adult Toxoplasmosis: A Previously Unrecognized Disease Entity Simulating the Typhus-Spotted Fever Group, J. A. M. A. **116**: 807 (March 1) 1941.
13. Sabin, A. B.: Toxoplasmic Encephalitis in Children, J. A. M. A. **116**: 801 (March 1) 1941.
14. Sabin, A. B., and Warren, J.: Therapeutic Effectiveness of Certain Sulfonamides on Infection by an Intracellular Protozoon (Toxoplasma), Proc. Soc. Exper. Biol. & Med. **51**: 19, 1942.
15. Warren, J., and Sabin, A. B.: Effect of Certain Antiprotozoal Drugs on Toxoplasma in Vitro and in Vivo, Proc. Soc. Exper. Biol. & Med. **51**: 15, 1942.
16. Warren, J., and Sabin, A. B.: The Complement Fixation Reaction in Toxoplasmic Infection, Proc. Soc. Exper. Biol. & Med. **51**: 11, 1942.

also studied the complement fixation reaction in toxoplasmic infection. Sabin and Ruchman [17] investigated the characteristics of the Toxoplasma-neutralizing antibody in monkeys and human beings.[18] Heidelman [19] evaluated the Toxoplasma-neutralizing antibody test in patients with chorioretinitis. The ocular lesions of toxoplasmosis were studied by Koch and his co-workers [20] and by Heath and Zuelzer [21] and by others.[22] The radiologic observations in toxoplasmosis were described by Sante,[23] by Dyke and his co-workers [24] and by others. Excellent reviews of the subject were published by Sabin,[3b] Weinman [25] and by Callahan, Russell and Smith.[26]

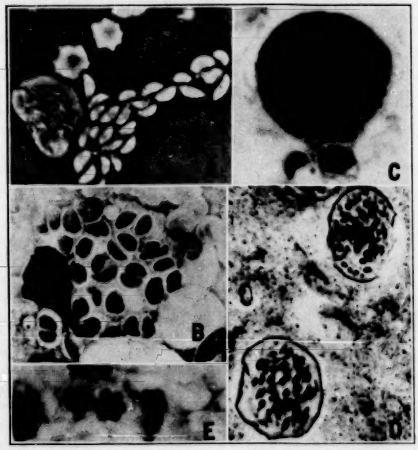


Fig. 1.—*A*, Toxoplasma, fresh preparation from peritoneal exudate of mouse; showing organisms free and within macrophage, also crenated red blood corpuscles. Phase-contrast microscope. *B*, Toxoplasma, Giemsa stain. *C*, Toxoplasma pseudocyst in neuron of substantia nigra (case B.D.A.) (hematoxylin and eosin). *D*, Toxoplasma pseudocysts impregnated with silver by Wilder's method. The argyrophilic cyst wall and its rigidity, indicated by the ragged tearing, may be noted. *E*, Toxoplasma, proliferative organisms in brain (case B.D.A.) (hematoxylin and eosin). (All illustrations × 960).

About 35 cases of toxoplasmosis in human beings have been reported to date, diagnosed by either autopsy or animal inoculation. Cases of chorioretinitis associated with serologic evidence of toxoplasmosis have been added to these. Infections in both human beings and animals have been reported from all over the world.[27]

PATHOGENESIS OF TOXOPLASMOSIS

*Acute Toxoplasmosis.*—The acute infection is a generalized one,[28] involving every organ, although lesions may be only microscopic in character. Toxoplasma has been observed to proliferate intracellularly in many types of cells. It is perhaps most frequently found in macrophages, fibroblasts, reticular cells and sinusoidal lining cells, in pulmonary alveolar lining cells, and in smooth muscle and cardiac muscle cells. Smaller or larger areas of necrosis may be associated with Toxoplasma. As a cellular response macrophages and lymphoid cells predominate over amphophilic granulocytes. In the central nervous system both neuronal and microglial elements may contain the organisms, and the microglial nodule is the typical response to injury. Most frequently encountered are: interstitial pneumonitis, myocarditis, encephalitis, splenitis, hepatitis and orchitis. Clinically the pulmonary or meningoencephalitic symptoms may be more prominent, and a cutaneous rash, and icterus due to hepatitis, are of frequent occurrence.

The numbers of organisms present, the degree of necrosis and the intensity of the cellular reaction in animals were observed to be variable, depending on the host as well as on the strain of Toxoplasma. Too few cases in human beings have been studied pathologically during the acute stage of the disease to evaluate the factors operating in the production of different

Fig. 2.—Microglial nodule in subcortical white matter (case R.F.). Note hypertrophic microglia in periphery and ameboid microglia in the center of the nodule. The vascular perithelium is proliferating (formaldehyde-Penfield's silver carbonate, × 325).

17. Sabin, A. B., and Ruchman, I.: Characteris ics of the Toxoplasma Neutralizing Antibody, Proc. Soc. Exper. Biol. & Med. **51**: 1, 1942.

18. Sabin, A. B.: Toxoplasma Neutralizing Antibody in Human Beings and Morbid Conditions Associated with It, Proc. Soc. Exper. Biol. & Med. **51**: 6, 1942.

19. Heidelman, J. M.: Evaluation of Toxoplasma Neutralization Tests in Cases of Chorioretinitis, Arch. Ophth. **34**: 28 (July) 1945.

20. Koch, F. L. P.; Wolf, A.; Cowen, D., and Paige, B. H.: Toxoplasmic Encephalomyelitis: VII. Significance of Ocular Lesions in the Diagnosis of Infantile, or Congenital, Toxoplasmosis, Arch. Ophth. **29**: 1 (Jan.) 1943.

21. Heath, P., and Zuelzer, W. W.: Toxoplasmosis: Report of Ocular Findings in Infant Twins, Arch. Ophth. **33**: 184 (March) 1945.

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23. Sante, L. R.: Roentgen Manifestations of Adult Toxoplasmosis, Am. J. Roentgenol. **47**: 825, 1942.

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25. Weinman, D.: Human Toxoplasma, Puerto Rico J. Pub. Health & Trop. Med. **20**: 125, 1944.

26. Callahan, W. P., Jr.; Russell, W. O., and Smith, M. G.: Human Toxoplasmosis: A Clinicopathologic Study with Presentation of Five Cases and Review of the Literature, Medicine **25**: 343, 1946.

27. Magnusson, J. H., and Wahlgren, F.: Human Toxoplasmosis: An Account of Twelve Cases in Sweden, Acta path. et microbiol. Scandinav. **25**: 216, 1948. Winsser, J.; Verlinde, J. D.; van Thiel, P. H.; Davel, J., and van der Elst, P.: Isolation of Toxoplasma from Cerebrospinal Fluid of a Living Infant in Holland, Proc. Soc. Exper. Biol. & Med. **67**: 292, 1948.

28. (*a*) Paige, Cowen and Wolf,[3a] case 5. (*b*) Pratt-Thomas, H. R., and Cannon, W. M.: Systemic Infantile Toxoplasmosis, Am. J. Path. **22**: 779, 1946. (*c*) Pinkerton and Henderson.[12] (*d*) Pinkerton and Weinman.[14]

degrees of organ involvement. The age of the patient appears to be of importance, since infants show more severe and extensive lesions at autopsy than do adults. It is important to keep in mind that the acute stage of the infection may be relatively or entirely asymptomatic, especially so in adults, and need not cause disease.

Fig. 3.—Microglial nodule in mouse brain. The cells are better outlined since fixation was prompt and more appropriate to the silver technic (formaldehyde ammonium bromide, Hortega's silver carbonate, × 162).

*Subacute Toxoplasmosis.*—This terminology is used to designate the cases in which there are regressing lesions in the extraneural viscera, whereas in the central nervous system and the eyes Toxoplasma continues to proliferate actively. Most of these patients acquired toxoplasmosis antenatally or neonatally, suggesting a low degree of resistance of fetuses and infants to Toxoplasma. The majority of neonatal cases of toxoplasmosis fall into this group. Here one sees in extraneural tissue evidence of past acute infection in the form of focal accumulations of lymphocytes, plasma cells and eosinophilic granulocytes. Fibroblasts are proliferating and are organizing areas of necrosis. Toxoplasma is not encountered in these foci.

The central nervous system presents a completely different picture. The basic lesion, the microglial nodule, is of common occurrence, and Toxoplasma is frequently found associated with it. These microglial nodules have been termed granulomas by most other authors,[29] supposedly consisting of accumulations of epithelioid cells and thought to be derived from hyperplastic endothelial and adventitial cells from the vessel walls as well as possibly from large hematogenous mononuclear cells.[10] In my hands, appropriate methods of silver impregnation showed these lesions to be made up of microglial cells in both human and animal material (figs. 2 and 3). These microglial cells are derived from preexisting microglia and from perithelial cells, but no significant endothelial proliferation was found. Furthermore, the hypertropic microglia of the nodules present a different appearance from epithelioid cells of a tuberculoma in neural tissue.

The disappearance of Toxoplasma from the extraneural viscera can best be explained on the basis of acquired immunity. Equivocal neutralizing antibody reactions, thought to be due to low titers of antibody, were obtained with the serums of 2 patients [30] succumbing with subacute toxoplasmosis. The persistent proliferation of Toxoplasma within the central nervous system may be explained by the observed poor diffusion of serum antibody into brain substance. This has previously been observed for bacterial antibody [31] and viral antibody [32] in rabbits where the ratio of serum antibody content versus brain antibody content, versus cerebrospinal fluid antibody content, was approximately equivalent to 300:3:1. It is of interest to note that the serum-cerebrospinal fluid antibody ratio parallels the protein content of the two fluids (6,000:20 mg. per hundred cubic centimeters), thus perhaps explaining this apparent "blood-brain-barrier" on the basis of a differential diffusion gradient for proteins. Differential Toxoplasma-neutralizing antibody titers have been

Fig. 4.—*A*, cross section of brain (case B.D.A.) showing periventricular zones and degeneration of white matter (phosphotungstic acid hematoxylin × about 93/100). *B*, close-up of right ventricle. The periventricular zones are absent where ependymal lining (choriod plexus) has been preserved (phosphotungstic acid hematoxylin × about 4½).

29. (*a*) Wolf and Cowen.[10] (*b*) Callahan, Russell and Smith.[20] (*c*) Sabin.[20a] (*d*) Zuelzer, W. W.: Infantile Toxoplasmosis, with a Report of Three New Cases, Including Two in Which the Patients Were Identical Twins, Arch. Path. **38**: 1 (July) 1944.

30. Zuelzer,[28d] case 2. Frenkel and Friedlander,[18] case B.D.A.

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32. Morgan, I. M.; Schlesinger, R. W., and Olitsky, P. K.: Induced Resistance of the Central Nervous System to Experimental Infection with Equine Encephalomyelitis Virus, J. Exper. Med. **76**: 357, 1942.

demonstrated in human serum, peritoneal fluid, brain and cerebrospinal fluid.[33]

The other characteristic and unique lesion in the central nervous system is the periventricular reaction zone (figs. 4 and 5 *A*). This zone surrounds the lateral and third ventricles, wherever the ependymal epithelium has been denuded. Proceeding from the relatively unchanged brain tissue lumenally, this reaction zone may be conveniently described as consisting of four subzones of (1) cellular infiltration and thrombosis of capillaries, (2) thrombosis of large vessels, (3) cellular necrosis and (4) repair. The first subzone shows much microglial proliferation, necrobiosis of

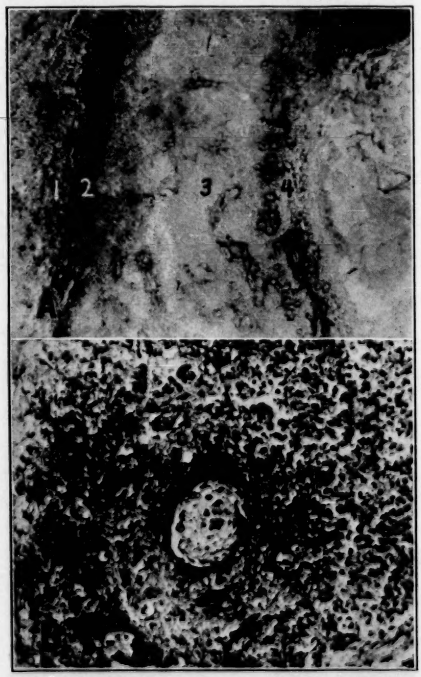


Fig. 5.—*A*, periventricular reaction zone, with the four subzones (1) of cellular infiltration and thrombosis of capillaries, (2) of thrombosis of large vessels, (3) of cellular necrosis and (4) of repair (phosphotungstic acid hematoxylin × about 19½). *B*, periventricular subzone 2, showing fibrin exudation (black) surrounding a thrombotic vessel (formaldehyde-phosphotungstic acid hematoxylin × about 300).

astrocytes and neuronal cells, as well as much perivascular lymphocytic and granulocytic infiltration accompanying the damaged capillaries. The second subzone, of vascular thrombosis, is characterized by pronounced perivascular fibrin exudation, mural edema and plasma cell infiltration (fig. 5 *B*). The third subzone is marked by necrosis involving all cells excepting fibroblasts in the walls of certain large vessels. The fourth subzone, of repair, is formed by proliferating fibroblasts and small vessels that are derived from certain large vessels which have not undergone complete thrombosis in the outer three subzones. Numerous plasma cells and adventitial wandering cells as well as Toxoplasma, both viable and degenerating forms, are found here. Calcium salts have been deposited throughout the third periventricular subzone and in bands of degenerating Toxoplasma in the fourth one.

The ventricular foramens of Monro and the aqueduct are blocked by inflammatory exudate. The ventricular lumens contain fluid of high protein content (1,000 to 2,600 mg. per hundred cubic centimeters), which cannot escape. Toxoplasma is frequently found in this ventricular fluid, which has been shown to contain Toxoplasma antigen (v.i.). If one recalls the aforementioned evidence for the presence of Toxoplasma-neutralizing antibodies in the serum, the zone of necrotizing vasculitis surrounding the antigen-containing ventricles strongly suggests this zone to be the site of an antigen-antibody reaction.

The necrotizing vascular reaction may be explained by antigen and antibody reacting in the scanty intercellular fluid and on the surface of the mural cells, thereby damaging the latter. Whatever small amount of blood reaches the fourth subzone contains less antibody, since much of it has been neutralized in passage through the outer zones. Furthermore, the proliferating fibroblasts in this fourth zone form a loose type of connective tissue, the interstices of which are filled with much antigen-containing fluid. This allows any remaining serum antibody to be neutralized in a liquid medium and in less contact with cells. The necrotizing vasculitis previously described bears considerable resemblance to the necrotizing allergic reaction, according to Bohrod's[34] classification. Ependymal epithelium covering the ventricular walls and the choroid plexus tufts seem to form an effective barrier for the ventricular fluid seepage into the surrounding tissue where it can come into contact with vascular channels containing antibody. Desquamation of a few choroid plexus lining cells gives rise to a formation of fibrinoid collagen in the plexus stroma. In summary, the periventricular reaction zone resembles an antigen-antibody reaction in vivo, analogous to a reaction of hypersensitivity. This lesion appears to have no exact parallel in any other infection.

The high protein content of the ventricular fluid (up to 2,600 mg. per hundred cubic centimeters), mentioned previously, is derived in part from the plasma that permeated the damaged vascular walls and in part from necrotic brain tissue that desquamated into the ventricles. The protein level of the subarachnoid fluid is lower, usually between 100 and 600 mg. per hundred cubic centimeters. It is in nearer to normal equilibrium with the blood stream owing to drainage and the vascularity of the meninges.

The clinical signs and symptoms of subacute toxoplasmosis, such as hydrocephaly and convulsions, are readily explained by the lesions described. Cerebral calcifications are usually small or even microscopic and may not be detectable radiologically. Chorioretinitis, however, is the most consistent clinical observation of the neonatal subacute disease, and it has been found in virtually every patient when it was looked for. Both exudative and proliferative types of retinitis and iridocyclitis have been encountered. The choroid usually shows less involvement and more chronic inflammation than the retina. A vitreous exudate is usually associated with the active retinal lesions, thus obscuring

33. Frenkel, J. K.: Unpublished data.

34. Bohrod, M.: Classification of the Histologic Reactions in Allergic Diseases, Am. J. Med. **3**: 511, 1947.

the latter on fundoscopic examination. Toxoplasma organisms are found in the retinal lesions, frequently in the form of pseudocysts.

The subacute retinitis is analogous to the cerebral lesions, the retina being of neuroectodermal derivation. The ocular fluids contain an amount of protein similar to the cerebrospinal fluid (normal range 15 to 30 mg. per hundred cubic centimeters), hence similarly low antibody levels may be assumed to exist in the latter two fluids, as compared with the blood serum. The continued proliferation of Toxoplasma in the retina may therefore be analogous to the persistent proliferation of the organisms in the central nervous system. In the latter case, evidence has been presented that it proceeds because of the low level of specific antibodies present in that location.

Symptomatic subacute toxoplasmosis frequently has a fatal outcome, but surviving patients have been observed. Signs and symptoms in the surviving patients are variable, depending on the severity of lesions present. Chorioretinitis again is the most outstanding sign and may cause decided visual impairment if the macular area is involved. Since most of these patients at the time of their observation were in the chronic stage of the disease, they will be presented later.

*Chronic Toxoplasmosis.*—This terminology is used in reference to cases with clinical or laboratory evidence of toxoplasmosis without signs of widespread activity. Since no reports of autopsy of previously symptomatic patients are available and since Toxoplasma has not been isolated from any such cases of chronic disease, the crucial question of whether there is persistence of Toxoplasma, hence true chronicity, must remain only partially answered. There is much evidence, however, to favor the hypothesis of a chronic state of toxoplasmic infection in human beings. On several occasions, structures resembling Toxoplasma pseudocysts (fig. 1 *C* and *D*) have been found in routine autopsy material.[35] The recurrence of active chorioretinitis in patients showing the scars of subacute toxoplasmosis can best be explained by the hypothesis of Toxoplasma persisting through a latent stage. Finally, chronic latent toxoplasmosis has been demonstrated to occur in mice,[36] rats,[2b] guinea pigs and rabbits [37] and hamsters.[33] Certain of these animals were found to have a chronic latent infection which had been acquired in nature, while in others this state has also been demonstrated experimentally. Depending on the virulence of the Toxoplasma strain as well as on the degree of host resistance (and hence the duration of the subacute stage of infection), fewer or larger numbers of Toxoplasma pseudocysts are found in the central nervous system and the eyes of such animals with chronic latent disease.[33] These pseudocysts may persist for considerable periods, probably for many years. An argyrophilic cyst wall (fig. 1 *D*) has been demonstrated on them,[33] which is probably the reason that they usually do not evoke a cellular reaction. However, the presence of small foci of necrosis and of microglial proliferation in animals with the chronic disease suggests the possibility of the rupture of such pseudocysts, with the release of antigenic material in the form of organisms and other proteins. Whereas chronic toxoplasmosis may be clinically and pathologically latent, reactivation may occur secondary to rupture of pseudocysts.

The failure to isolate Toxoplasma from the brain of monkeys that have passed through the acute stage of the infection [38] and from the brain of an asymptomatic patient who showed, in results of cutaneous and serologic tests, evidence of past toxoplasmic infection [33] might indicate that chronic latent toxoplasmosis may be of rare occurrence in primates. However, these few experiments cannot be regarded as conclusive. The numbers of organisms persisting in the brain of a relatively resistant host may be very small, so that, after grinding, Toxoplasma liberated from the protective pseudocyst wall may be inactivated even by the small amount of neutralizing antibody present in the unperfused brain. The brain of the patient just mentioned possessed slightly greater Toxoplasma-neutralizing capacity than her cerebrospinal fluid.[33] In contrast, the number of Toxoplasma pseudocysts in the central nervous system of rodents may be large enough to be found on routine microscopic brain sections. Their complete neutralization would be of less likely occurrence, because of the quantitative relationships between organisms and antibody.

Clinical signs and symptoms of past or persistent (chronic) toxoplasmosis may be variable according to the amount of damage produced during the acute and subacute stage of the disease. In symptomatic patients, chorioretinitis is the most frequent sign, followed in incidence by electroencephalographic evidence of cerebral damage, cerebral calcifications demonstrable radiologically and other signs, such as microcephaly, hydrocephaly, ocular malformations, spastic paraplegia and their associated symptoms. The significance of toxoplasmosis in the causation of anterior uveitis has not been clearly established. The rupture of a pseudocyst within the retina is suggested as the causative mechanism of recurrent acute chorioretinitis in patients with laboratory evidence of toxoplasmosis. The antigen liberated gives rise to a hypersensitivity reaction, characterized clinically by the exudative and hemorrhagic phenomena of "granulomatous posterior uveitis." [39] Since this reaction may persist for a prolonged period of time, it may be assumed, first, that antigen has been released into the retina and vitreum, whence absorption and neutralization would occur relatively slowly, and, secondly, that Toxoplasma might proliferate within the retina for some time, again releasing more antigen. As has been mentioned before, Toxoplasma-neutralizing antibody levels may be expected to be as low in the ocular fluids as in the cerebrospinal fluid, since the protein content of these two fluids is similar. Of 28 patients with "granulomatous chorioretinitis" studied by me,[40] 20, or 71 per cent, showed evidence of toxoplasmosis in results of cutaneous and serologic tests. The mean age of these patients when first seen was 23 years; their mean age when symptoms or signs were first noted was 13 years, whereas lesions most likely were

35. Kean, B. H., and Grocott, R. G.: Asymptomatic Toxoplasmosis, Am. J. Trop. Med. **27**: 745, 1947. Plaut, A.: The Problem of Human Toxoplasma Carriers, Am. J. Path. **22**: 427, 1946.

36. (*a*) Findlay and Middleton.[2a] (*b*) Weinman, D.: Chronic Toxoplasmosis, J. Infect. Dis. **73**: 85, 1943.

37. Perrin, T. L.: Toxoplasma and Encephalitozoon in Spontaneous and in Experimental Infections of Animals: A Comparative Study, Arch. Path. **36**: 568 (Dec.) 1943.

38. Sabin and Ruchman.[32] Frenkel.[33]

39. Woods, A. C.: The Influence of Hypersensitivity on Endogenous Uveal Disease (The Jackson Memorial Lecture), Am. J. Ophth. **20**: 257, 1947.

40. Frenkel, J. K.: Uveitis and Toxoplasmin Sensitivity, Proceedings Association for Research in Ophthalmology, Seventeenth Meeting, 1948, Am. J. Ophth., to be published.

present at a much earlier age in many of them. Fourteen of the 20 patients (70 per cent) were female.

Evidence for the occurrence of asymptomatic (and later chronic?) toxoplasmosis has been accumulated from the serologic observations associated with dermal hypersensitivity to Toxoplasma antigen. A survey conducted by me at the University of California Medical School revealed an incidence of 10 per cent in a group of 50 normal persons between the ages of 20 and 35 years and an incidence of 28 per cent in a group of 50 hospital patients between 50 and 83 years of age. None of these patients had any of the recognized clinical signs of toxoplasmosis, and from only 1 was a history of encephalitic symptoms elicited. Whereas the incidence of past (or persistent?) toxoplasmosis increases with age, signs and symptoms of the disease appear to be mainly connected with infection occurring during fetal life or in childhood. Most of the mothers who have given birth to infected infants have shown laboratory evidence of past toxoplasmic infection; however, none were recorded as having had symptoms suggestive of an acute infection, except for such acute respiratory and gastroenteric diseases that are prevalent in the population as a whole. It is likely, therefore, that acute toxoplasmosis may be asymptomatic in resistant persons (especially in adults) or that it might be accompanied with nonspecific signs and symptoms, suggesting "flu," a gastrointestinal upset, infectious mononucleosis or the like.

*Transplacental Toxoplasmosis.*—Direct evidence of the antenatal inception of toxoplasmosis was brought forth by Paige, Cowen and Wolf,[3a] whose fourth patient had intrauterine hydrocephalus necessitating craniotomy for delivery. Autopsy showed advanced subacute toxoplasmosis. Indirect evidence has been accumulated in the several cases reported with neonatal manifestations of widespread and advanced organ involvement characteristic of the subacute disease. The question arises as to whether the mother's initial infection with Toxoplasma was contracted during pregnancy or whether she had a chronic latent infection, in the course of which a few organisms escaped from a ruptured pseudocyst, infecting the placenta and hence the fetus. While either of these possibilities appear possible, primary infection of the pregnant mother appears more likely to be the commoner mode of fetal toxoplasmic infection. There is no history of a mother's transferring the disease in more than one pregnancy. None of the mothers with preexisting clinical signs and laboratory evidence of toxoplasmosis subsequently gave birth to infected infants. Conversely, none of the mothers who gave birth to toxoplasmic infants had any signs of the disease, except in 1 case of Heidelman's[19] (case 27), in which chorioretinitis in both the mother and the child was associated with Toxoplasma-neutralizing antibodies. However, the mother's only lesion was active eight years after the birth of the infant and there was no evidence that the lesion had been acquired before that pregnancy. The presence of a pronounced hypersensitivity to Toxoplasma after the acute infection makes blood stream dissemination of the organism rather unlikely.[41]

Furthermore, the grouping of cases in as rare a disease appears worthy of mention. Patients C. J. and B. D. A., observed by me,[4] were born on the same day in San Francisco, without any cases having been recognized in the succeeding eighteen months in several hospitals of this city. The 2 patients reported by Sabin (1941) showed symptoms of the disease within ten days of each other in adjacent localities. Zuelzer's patients reported in 1944 were born in Detroit within a week of each other. Pinkerton and Henderson's (1941) cases occurred during the same summer in St. Louis. These data might be interpreted as being indicative of minor epidemics of toxoplasmosis, leading to acute infection of the mothers. With the mode of adult infection not yet definitely established, one can only speculate on an epizootic among arthropod vectors.

### DIAGNOSIS OF TOXOPLASMOSIS

The isolation of Toxoplasma from a patient is the most significant single datum in the establishment of the diagnosis. Unfortunately, isolation is frequently not possible, leaving one to resort to pathologic, immunologic and serologic methods to confirm impressions gleaned from a patient's history and physical findings. Attempting to base a diagnosis only on one or the other finding appears to be premature in the present state of knowledge of the disease. It is highly desirable that one investigate patients completely, employing every method available, to arrive at a better understanding of the clinical syndromes. The lesions produced and the resulting signs and symptoms have been discussed in the previous sections. In the following section, an attempt will be made to evaluate the available laboratory aids.

*Isolation of Toxoplasma.*—During the acute stage of the infection, organisms might be recovered from blood, bone marrow, splenic puncture material, cerebrospinal fluid and possibly sputum. During the subacute stage organisms have been found in the ventricular fluid obtained by aspiration and from the central nervous system at autopsy. In the chronic state organisms might be present in the central nervous system, the eye and the myocardium. Visual demonstration of Toxoplasma on direct smears is rarely successful, except in the case of ventricular fluid sediments, where organisms have been demonstrated on several occasions during the subacute stage of the infection. Animal inoculations to study the biologic characteristics of the strain are highly desirable. Since chronic latent toxoplasmosis has been observed in many laboratory animals, it becomes necessary to utilize several species in each isolation attempt. Furthermore, the stock animals should be tested for the presence of such chronic latent infection by "blind passage" of their organs (especially brain) to other animals.

The following procedures were most useful in my hands for the isolation of Toxoplasma from human or animal sources. The inoculum, such as ventricular fluid sediment, is injected into groups of mice, hamsters and guinea pigs. One group of 4 to 6 animals of each species is inoculated intracerebrally, and a like group is inoculated intraperitoneally. If any of the animals should die, the brain is removed aseptically from animals inoculated by either route and it is subinoculated

41. Recently, Doctor C. D. Binkhorst reported from Holland the concurrence of chorioretinitis in a mother and her daughter (Toxoplasmosis, a monograph, Leiden, Netherlands, H. E. Stenfert Kroese, 1948, case 11; Ophthalmologica **115**: 65 [Feb.] 1948 [case 21]). Ocular lesions were first observed in the otherwise normal child at the age of 5 months; her serum contained Toxoplasma-neutralizing bodies when she was 6 years old. It was impossible to determine whether her infection was acquired in utero. Her mother's chorioretinitis is not typical for toxoplasmosis, and the result of her neutralizing antibody test was doubtful.

into other animals. At the same time impression films are prepared, stained with Wright's stain and examined for Toxoplasma (fig. 1 *B*). Intraperitoneally inoculated animals are examined for peritoneal exudate on the sixth and tenth days after injection. They are lightly etherized, and an abdominal paracentesis is performed with a 20 gage needle attached to a 2 cc. syringe. The pooled fluid, which must be obtained under aseptic conditions, is subinoculated intracerebrally into groups of fresh mice, hamsters and guinea pigs. The fluid is then examined either fresh or on a stained film for the presence of Toxoplasma. In the case of death of an intraperitoneally inoculated animal, impression films should be prepared from the mesentery, the liver, spleen and lung, and searched for Toxoplasma. If none of the animals should have ascites or die within one month, the survivors must be examined for infections that passed asymptomatically because of the low pathogenicity of certain (unadapted) strains. Half of the animals of each group are killed after one month and their brains pooled and subinoculated. This single "blind passage" frequently will bring to light a toxoplasmic infection present, although occasionally two or more such passages may be needed. The other half of the first inoculated animals should be held until the "blind passage" experiment has been carried to a definite conclusion. They may then be tested for immunity if an organism has been isolated. Most of these animals should be immune to a challenge injection with the homologous strain, although immunity to a heterologous virulent strain may be less pronounced (especially in mice).[42]

*Pathologic Examination.*—During the course of the acute infection, biopsies of skin, lymph node, bone marrow, liver and spleen may be available. From patients in the subacute stage ventricular fluid sediment may be obtained and treated like a "button." Various tissues may be available from autopsies of patients in any of the stages of the disease. Toxoplasma are easily recognizable in sections stained with hematoxylin and eosin or with one of the polychromic methylene blue dyes. Fixation of tissues in Zenker-formaldehyde is preferable to formaldehyde if cytologic detail is appreciated. Contrary to their elongate appearance in the fresh state or on the dry film, on sections Toxoplasma are usually rounded up and nearly spherical bodies of equal size (fig. 1 *C* and *E*). Great care must be exercised to distinguish Toxoplasma from organisms such as Histoplasma capsulatum, Trypanosoma cruzi, Leishmania, Encephalitozoon and Sarcocystis.[43]

*Antigenic Test for the Demonstration of Toxoplasma Antigen in Ventricular Fluid of Infants with Hydrocephalus.*[4b]—Fluids obtained from ventricular puncture of patients with subacute toxoplasmosis are centrifuged. One-tenth cubic centimeter of the supernatant is injected intradermally into normal guinea pigs and into guinea pigs with chronic latent toxoplasmosis. Ventricular fluids from 2 patients from whom Toxoplasma was isolated evoked after twenty-four hours a large area of erythema and induration at the site of injection in the infected guinea pigs. Little or no similar reaction was present in the normal animals. Ventricular fluids from 4 other hydrocephalic infants without evidence of toxoplasmic infection gave negative reactions in both infected and control groups.

On the other hand, ventricular fluid from a patient with Escherichia coli meningitis evoked a slight area of erythema and induration in the toxoplasmic guinea pigs, but none in the normal controls. Guinea pigs previously injected with human brain or cerebrospinal fluid may not be used, since they show pronounced reactions of dermal hypersensitivity on reinjection with the like material. This test, carefully used, may facilitate a rapid differential diagnosis of neonatal hydrocephalus.

*Cutaneous Tests with Toxoplasma Antigen (Toxoplasmin).*—This test [4b] is the most useful simple aid in the diagnosis of past or latent toxoplasmosis, whenever isolation of the causative organism is not feasible. Intradermal injection of suitable dilutions of toxoplasmin evoke reactions of a delayed (tuberculin) type of hypersensitivity in certain patients. Since 1945 about 300 persons have been investigated for toxoplasmin sensitivity, and high rates of positivity have been found in patients with chorioretinitis, in mothers who have given birth to infected children and others. There is a good correlation between the results of cutaneous tests and Toxoplasma-neutralizing antibody tests. When the result of a toxoplasmin cutaneous test is positive, it is usually followed by the appearance of complement-fixing antibodies to Toxoplasma antigen, whereas a negative result does not seem to give rise to such antibodies.

The cutaneous test is most useful in the diagnosis of chronic toxoplasmosis. Patients with acute toxoplasmosis are not expected to acquire dermal hypersensitivity early enough to be diagnostically useful. The test requires further trials in patients with the disease in the subacute stage to evaluate its diagnostic efficiency.

The diagnostic antigen [4b] is derived from the sediment of mouse peritoneal fluids rich in Toxoplasma. The organisms are inactivated, their cell bodies are broken up and the antigen is standardized, tested for sterility and diluted in phenolized saline solution. A control antigen is similarly treated. Both antigens are injected intradermally in amounts of 0.1 cc. Readings are obtained after forty-eight to seventy-two hours, but positive reactions usually are apparent after twenty-four hours. An area of erythema and induration of over 10 mm. with a negative reaction in a control is taken as evidence of past or persistent infection. The intensity of the positive reaction could not be correlated with the degree of clinical activity.

*An in Vitro Test for Hypersensitivity to Toxoplasma Antigen.*—Recently Nantz and Blatt [44] described a method for the evaluation of bacterial hypersensitivity by the application of a tissue culture technic. Their method permits a quantitative analysis of hypersensitivity exhibited by a patient's white blood cells toward a variety of antigens. At present, studies are under way to evaluate the usefulness of this test in the study of toxoplasmic infection.

*Toxoplasma-Neutralizing Antibody Test.*—This test, first described by Sabin and Ruchman,[45] has been

42. I shall be pleased to investigate immunologically and serologically the relationships of freshly isolated strains to strains of Toxoplasma carried by me.

43. Perrin.[37] Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases: An Atlas, Philadelphia, W. B. Saunders Company, 1945, p. 204.

44. Nantz, F. A., and Blatt, H.: The Application of a Tissue Culture Technique in the Clinical Evaluation of Bacterial Hypersensitivity, Ann. Allergy **5**: 554, 1947.

45. Sabin and Ruchman.[37] Sabin.[38]

widely used and has proved useful in demonstrating such antibodies as may be found in the subacute and the chronic state of the infection. However, equivocal readings are frequently obtained, apparently because of low titers of neutralizing antibodies.[46] The antibody titer usually increases after a positive reaction to a toxoplasmin cutaneous test; hence it is useful to employ these two tests in conjunction. Other disadvantages of the neutralizing antibody test include the fact that diagnostic readings require a week to develop and that neutralizing antibodies are unstable both at room and refrigerator temperatures, necessitating storage of test serums in the frozen state. For the performance of the test an active strain of Toxoplasma must be maintained in the laboratory. Neutralizing antibodies are demonstrated by their inhibiting effects in Toxoplasma-serum mixtures on the development of papulonecrotic cutaneous lesions in rabbits, at the sites of intradermal injection of various dilutions of Toxoplasma.[47] Recently Alm [48] demonstrated neutralizing antibodies quantitatively on infected chorioallantoic membranes of chick embryos. Since chronic active toxoplasmosis is frequently accompanied by relatively low levels of neutralizing antibodies, it is of interest to check for increase of antibody titers during treatment. Although the serum antibody measured here is not directly related to the degree of dermal hypersensitivity, analogous qualitative results are usually obtained. The patients who give divergent results with these two tests, however, are most interesting to study for possible pathologic implications of this phenomenon.

*Toxoplasma Complement-Fixing Test.*—This test was first described by Warren and Sabin.[16] Recently an improvement of this technic was reported by Warren and Russ.[49] Dr. Carl M. Eklund and Dr. David Lackman performed complement fixation tests with Toxoplasma antigen on the serums of many of my patients using a still different technic. Two of their observations will be quoted here, since they are important for correlation with those observations obtained by use of the other tests. Patients who showed a negative toxoplasmin skin test on repeated occasions, did not possess demonstrable complement-fixing antibodies, nor did they develop any in result of these antigen injections. Secondly, patients with positive toxoplasmin skin tests, who usually did not show complement-fixing antibodies in their serum, frequently showed an antibody titer in response to the antigen injections. Pre-existing titers were increased. Titers tended to disappear between one and two years after the patient received the last antigen injection or gave birth to an infected infant. Many patients have shown a positive neutralizing antibody test whereas a complement-fixing test on their serum has been negative. Data obtained by the use of monkeys likewise indicate that the presence of a complement-fixing titer is indicative of a recent infection or of recent contact with Toxoplasma antigen. Judging from the animal data, complement-fixing titers might be detectable within a week after infection. Since at this time neutralizing antibodies cannot be demonstrated unequivocally, the complement-fixing test might prove especially useful in the early stage of the disease, if a rise in titer can be demonstrated (see, however, footnote 47). Its results should be compared, however, with those of the other tests, and, of course, an attempt should be made to isolate Toxoplasma.

*Clinical Laboratory Data.*—The most striking observation is the high ventricular fluid protein content in patients with subacute toxoplasmosis. No other consistent observations have been encountered, and further study is required to establish significant data.

### TREATMENT OF TOXOPLASMOSIS

In acute toxoplasmosis the number and severity of lesions are in direct proportion to the number and virulence of the organisms and inversely proportional to the natural resistance of the host. Treatment with sulfadiazine and sulfamerazine in full doses has been observed to control this type of infection in animals. Robinson [50] reported the successful treatment of a child with predominantly meningoencephalitic signs and symptoms. Treatment should be continuous for about two to three weeks, until sufficient immunity has been acquired to prevent a relapse. As has been shown by Weinman,[36b] treatment with sulfonamide drugs suppresses proliferation of organisms, but it does not rid the host of these organisms. Toxoplasma persists in the form of pseudocysts within neural tissue, and, since antibody titers are much lower there than in the serum the organisms might resume proliferation in the absence of a sufficiently high level of sulfonamide drugs or antibody. The clinical relapse observed by Robinson might be explained on this basis. Supportive treatment, such as oxygen, transfusions (if possible of serum containing neutralizing antibody) and a low fat diet, should be given as indicated. Penicillin,[51] streptomycin, and a number of other drugs [52] were not found effective in the treatment of toxoplasmosis. Recently, chloromycetin, aureomycin, subtilin, polymyxin-B, chlorguanide hydrochloride (paludrine®), bacitricin, p-aminosalicylic acid, nicotinic acid and nitrofurazone (furacin®) I found ineffective in treatment of experimental toxoplasmosis.

In subacute toxoplasmosis, extensive mechanical and usually irreversible lesions are present by the time the diagnosis is made. Indeed, hydrocephaly, being usually the first suggestive sign, depends on occlusion of the aqueduct and the ventricular foramens. Although treatment with sulfonamide drugs has proved effective in suppressing proliferation of the organisms, a patient observed by me (R. F.),[48a] died later with extensive central nervous system damage, accompanied with histologic signs of repair and very few organisms. Zuelzer [29d] has made similar observations, although 1 of his patients survived. In cases of more advanced disease, in which hydrocephaly and chorioretinitis are

46. Heidelman.[19] Frenkel.[9b]

47. An in vitro dye test has recently been developed which is a better tool for the estimation of Toxoplasma-neutralizing antibody. The quantitative data obtained by this test provide the most useful information for the serologic diagnosis of Toxoplasmosis. Furthermore, it was demonstrated that the Toxoplasma-neutralizing antibody itself is heat stable, that, however, a heat-labile "accessory factor" is necessary to consummate the neutralizing process, in the rabbit test as well as in the in vitro dye test (Sabin, A. B., and Feldman, H. A.: Dyes as Microchemical Indicators of a New Immunity Phenomenon Affecting a Protozoon Parasite [Toxoplasma], Science **108**: 660 [Dec. 10] 1948).

48. Alm, L.: Nagot om Toxoplasmosens Mikrobiologi, Svenska Läkartidning **45**: 333, 1948.

49. Warren, J., and Russ, S. B.: Cultivation of Toxoplasma in Embryonated Egg: An Antigen Derived from Chorioallantoic Membrane, Proc. Soc. Exper. Biol. & Med. **67**: 85, 1948.

50. Robinson, P.: A Case of Toxoplasmosis with Recovery, Ann. paediat. **168**: 134, 1947.

51. Augustine, D. L.; Weinman, D., and McAllister, J.: Rapid and Sterilizing Effect of Penicillin Sodium in Experimental Relapsing Fever Infections and Its Ineffectiveness in the Treatment of Trypanosomiasis (Trypanosoma lewisi) and Toxoplasmosis, Science **99**: 10, 1944.

52. Cross, J. B., and Anigestein, L.: Chemotherapeutic Study of Experimental Toxoplasmosis—Preliminary Report, Texas Rep. Biol. & Med. **6**: 260, 1948.

present, treatment with sulfonamide drugs does not appear to be very promising, and survival may be accompanied with such conditions as mental deficiency, partial or complete blindness, spastic paraplegia and convulsions.

In chronic active toxoplasmosis, lesions are thought to be due to rupture of Toxoplasma pseudocysts, such as in the retina, giving rise to localized reactions of hypersensitivity. Consideration of this concept, discussed previously, has led to attempts at desensitization of patients showing active chorioretinitis, associated with evidence of toxoplasmic infection from cutaneous and serologic tests. The rationale of this treatment implies stimulation of increased titers of free plasma and intercellular antibody, capable of binding and neutralizing the antigen in the intercellular fluids, and minimizing the amount of the same reaction taking place on the more vulnerable cell surfaces. High serum antibody levels should be obtained, since their diffusion ratio into the central nervous system and the eye is of very low order.

So far, 9 such patients have been treated by injection of graded increasing doses of Toxoplasma antigen, supplemented in some instances by nonspecific protein therapy with intravenous typhoid vaccine.[46] The lesions became inactive during treatment in 8 patients, as indicated by disappearance of the vitreous exudate, decreased retinal edema and infiltration and beginning pigment deposition. One patient was not improved, and granulomatous iridocyclitis developed in addition to the chorioretinitis. This latter patient also had a positive reaction to a tuberculin test. Since the course of these lesions cannot be predicted, any improvement occurring during treatment cannot necessarily be said to be due to it. The results of this experimental treatment are recorded here to point a way for careful and prolonged clinical research work, which should be controlled by the immunologic and serologic tests previously discussed.

Treatment with sulfonamide drugs does not appear to have a significant effect on Toxoplasma pseudocysts. The chorioretinal lesions are thought to be due more to the liberated antigen, which does not quickly diffuse out of the vitreous, than to proliferation of Toxoplasma in the retina. In persistent cases of chorioretinitis, treatment with sulfonamide drugs might be given a trial. However, again this treatment may be expected only to inhibit proliferation of organisms. What is needed is a drug that diffuses through the blood-neuroectodermal barrier into the brain and the eye and that kills Toxoplasma, rather than merely suppressing its multiplication.

SUMMARY

The classification proposed here is based primarily on the pathogenesis and secondarily on clinical manifestations of toxoplasmosis. Each infection is considered to progress from the acute, to the subacute, to the chronic stage, unless death supervenes. The laboratory tests most useful in the diagnosis of each stage are included in the following outline.

A. *Acute Toxoplasmosis.* Generalized, irrespective of age or mode of infection, involving all viscera, including the central nervous system; diagnosed by demonstration of the organisms (I), rise in complement fixation and neutralizing antibody[47] titers (I, II)

I. *Symptomatic*—pneumonitis, hepatitis, meningoencephalitis, cutaneous rash, etc.

(*a*) Early predominantly visceral symptoms

1. Infantile cases [28a, b]
2. Adult cases [53]

(*b*) Late predominantly meningoencephalitic symptoms:

1. Infantile cases [54]
2. Adult case [55]

II. *Asymptomatic*—majority of cases, undiagnosed

B. *Subacute Toxoplasmosis.* Depending on persistence and proliferation of Toxoplasma in the central nervous system, including the eye; subsidence of other visceral lesions due to antibody formation; zone of antigen-antibody reaction surrounding ventricles; diagnosed by isolation of Toxoplasma, antigenic test with ventricular fluid (I), rise in neutralizing antibody titer, positive complement fixation titer (I, II)

I. *Symptomatic*

(*a*) Fatal; chorioretinitis, usually with periventricular zones of necrosis, hydrocephaly, cerebral calcifications usually small or absent

(*b*) Surviving; chorioretinitis, usually with microcephaly, cerebral calcifications frequently larger, other signs of cerebral damage (electroencephalogram)

II. *Asymptomatic*—majority of cases, no significant lesions; undiagnosed

C. *Chronic Toxoplasmosis.* Depending on persistence of Toxoplasma pseudocysts in the central nervous system, the eye and the myocardium; diagnosed clinically by immunologic and serologic tests

I. *Active*—chorioretinitis, anterior uveitis (?); positive reaction to cutaneous test, positive reaction to neutralizing antibody test, positive or negative complement fixation titer

II. *Latent*

(*a*) Symptomatic—chorioretinitis, anterior uveitis (?), microphthalmia, other ocular malformations, microcephaly, hydrocephaly, spastic paraplegia; positive reaction to cutaneous test, positive reaction to neutralizing antibody test, positive or negative complement fixation titer

(*b*) Asymptomatic

1. Mothers who gave birth to infected infant; positive reaction to cutaneous test, positive reaction to neutralizing antibody test, complement fixation titer usually positive for several months thereafter
2. Pseudocysts discovered at autopsy
3. Only evidence: positive reaction to cutaneous test, positive reaction to neutralizing antibody test, complement fixation titer usually negative.

53. Pinkerton and Weinman.[11] Pinkerton and Henderson.[13]
54. Sabin.[13] Robinson.[50]
55. Guimarães, F. N.: Toxoplasmose humana: Meningoencefalomielite toxoplasmica; ocorrência em adulto e em recemnascido, Mem. Inst. Oswaldo Cruz **38**: 320, 1943.

**Radiation and Abnormal Children.**—The best evidence we have to date is that in humans, in general, radiation will *not* significantly increase the rate of these mutations. Our studies of the survivors of Hiroshima and Nagasaki (carried on by the Atomic Casualty Commission) thus far fail to disclose any increase whatever of abnormal children, nor has there, thus far, been any increased incidence of still births or miscarriages, or of leukemia. Our Commission will continue to support this extensive work in Japan, the results of which in the course of time will throw a great deal of light on this whole subject of radiation effects—immediate and long-term.—From an address by David E. Lilienthal, Chairman, Atomic Energy Commission, before the American College of Physicians, New York, March 31, 1949.

# CULDOSCOPY: ITS DIAGNOSTIC VALUE IN PELVIC DISEASE

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New York

Pathologic conditions of the female pelvis that do not permit a positive diagnosis by the routine methods are occasionally suspected or actually encountered. In the presence of inconclusive observations in conditions that require a positive diagnosis, exploration by laparotomy has frequently been employed. It is believed that any safe method of direct study of the pelvic viscera that avoids exposure by laparotomy deserves consideration.

## HISTORY

The value of endoscopic visualization is amply demonstrated by its frequent application to the body cavities and hollow viscera by specialists in many fields.

In 1910, Kelling [1] successfully visualized the abdominal viscera through an endoscope by means of abdominal puncture. Ruddock [2] in 1934 published a report of 900 patients examined by means of a peritoneoscope introduced through the anterior abdominal wall. Abdominal puncture, in the absence of ascites, regardless of the favorable reports of its advocates, has not gained widespread recognition. The critics of peritoneoscopy fear bowel injury, infection, pain associated with the puncture and the distention of the cavity with gas under positive pressure.

I have applied endoscopy to the pelvis by a technic that avoids the undesirable features of abdominal puncture. Endoscopy through the rectovaginal pouch, commonly termed the cul-de-sac of Douglas, accomplishes this purpose. The procedure is termed culdoscopy.

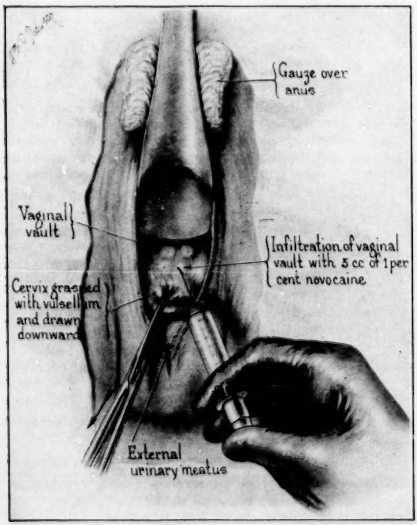
Gauze over anus
Vaginal vault
Infiltration of vaginal vault with 5 cc of 1 per cent novocaine
Cervix grasped with vulsellum and drawn downward
External urinary meatus

Fig. 1.—Posterior view of the vaginal canal, with the patient in the knee-chest position. Injection of local anesthetic in the vaginal vault.

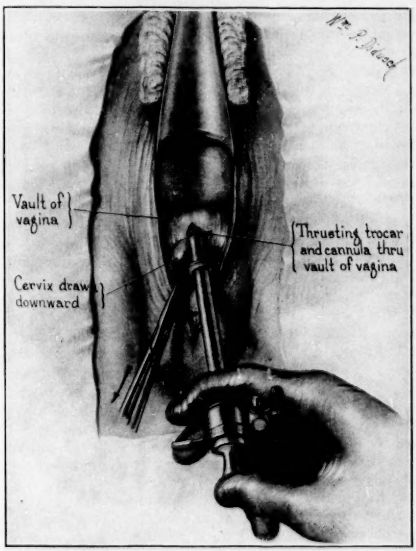


Fig. 2.—Posterior view of the vaginal canal, with the patient in the knee-chest position. The trochar is in the cannula, the tip poised over the vaginal vault ready for puncture.

## THE PUNCTURE

It is apparent that any complications or accidents that might occur during culdoscopy would result from the puncture rather than from visualization. It is the puncture, then, that must be critically considered.

The surgical anatomic relations of the rectovaginal pouch to the cervix and rectum in the knee-chest position account for the desirable features of culdoscopy. In the knee-chest position the movement of abdominal viscera cephalad creates a negative pressure in the abdominal cavity. This may amount to as much as 35 to 50 cc. of water. The intestines fall out of the pelvis. The posterior vaginal vault becomes exaggerated, stretches and is thinned out, so that it is frequently only a few millimeters in thickness. The vaginal mucous membrane and the peritoneum of the cul-de-sac approximate at the point of greatest concavity. The rectum is separated from the cervix by several centimeters. In this condition the vaginal vault may be easily punctured with needle or trochar with very little discomfort. The puncture is accompanied with the inrush of air which signalizes entry into the peritoneal cavity. A spontaneous pneumoperitoneum amounting to 800 to 1,600 cc. of air may result. Positive gas pressure is not required. Embolism and the extraperitoneal extravasation of air are thus avoided.

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Read before the Section on Obstetrics and Gynecology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 24, 1948.

1. Kelling, G.: Ueber die Moglichkeit die Zystoskopie bei Untersuchungen seröser Höhlungen anzuwenden, München, med. Wchnschr. **57**: 2358, 1910.

2. Ruddock, J. C.: Peritoneoscopy, West. J. Surg. **42**: 392, 1934.

The cul-de-sac has been punctured by me and by others [3] more than four hundred times with trochar and needle without serious complications.

## INSTRUMENT AND EQUIPMENT

A trochar and cannula have been devised to puncture the vaginal mucosa and peritoneum of the cul-de-sac by one thrust without preliminary incision. The cannula is large enough to admit an endoscope designed to view the pelvic organs.

The trochar is grooved and the cannula is equipped with a valve so that carbon dioxide may be introduced into the peritoneal cavity before the trochar is removed. A length of rubber tubing from a container of carbon dioxide may be attached to the cannula valve. When the valve is opened, the gas will be drawn into the peritoneal cavity until the negative pressure is neutralized. Self-retaining cervical cannulas of the screw tip and balloon type have been devised for the purpose of introducing a solution of indigo carmine through the uterus and tubes while they are being observed through the culdoscope.

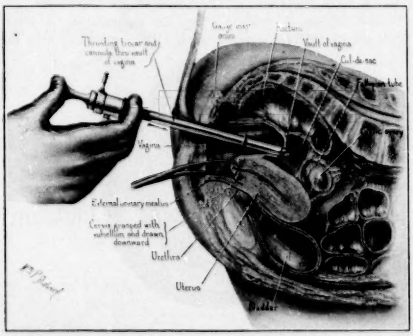


Fig. 3.—Sagittal section of the pelvis, with the patient in the knee-chest position. The posterior vaginal septum shown at the moment of puncture.

The examining table should be equipped with tall upright leg holders and shoulder braces. Muslin bandages or thigh straps are necessary to support the thigh against the leg holders. Other instruments required are an 8 inch (20 cm.) knee bent vulsellum, perineal retractor, 10 cc. syringe and a 4½ inch (11 cm.) 22 gage needle. Complete operating room facilities are not necessary. A convenient examining room will suffice.

## PREPARATION OF THE PATIENT

The vulva is shaved. The bladder and rectum are emptied. One hundred milligrams of meperidine hydrochloride may be given by hypodermic injection forty-five minutes before the examination. Three grains (195 mg.) of amobarbital sodium given orally one hour before the examination has often been satisfactory. In many cases the preexamination medication has been omitted.

## THE PROCEDURE

The patient is placed in the knee-chest position, maintained by shoulder braces, leg holders and thigh bandages. The vulva, buttocks and anal region are painted with a nonirritating antiseptic solution. The patient is draped with a sterile sheet or towels. The perineum is elevated with a perineal retractor. The retracting blade should be applied to the outer three fourths of the posterior vaginal wall. The cervix is grasped with a knee bent vulsellum and drawn down. The point of greatest concavity of the vaginal vault is infiltrated with three or four wheals of 2 per cent procaine hydrochloride, with a 10 cc. syringe and a 4½ inch (11 cm.) 22 gage needle. Five or six cubic centimeters of the anesthetic agent are sufficient. The

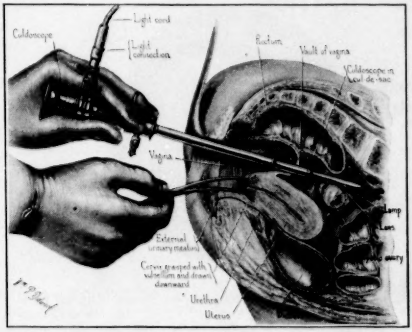


Fig. 4.—Sagittal section of the female pelvis, with the patient in the knee-chest position. The trochar has been removed and the culdoscope introduced through the cannula in position for visualization.

tip of the perineal retractor should be adjusted so that it does not extend into the vaginal vault. The perineum and distal three fourths of the posterior vaginal wall should be elevated as high as comfort will allow. The cervix should be drawn down only enough to accentuate the vaginal concavity and to steady the structures during puncture. Forceful traction on the cervix at this moment should be avoided. The trochar and cannula with the valve closed are then poised over the posterior vaginal wall at the point of greatest concavity. This point may be nearer the posterior vaginal wall and rectum than to the cervix. The trochar is then pushed through the vaginal wall with one quick thrust. When the valve on the cannula is opened or if the trochar is removed, air will be heard to enter the

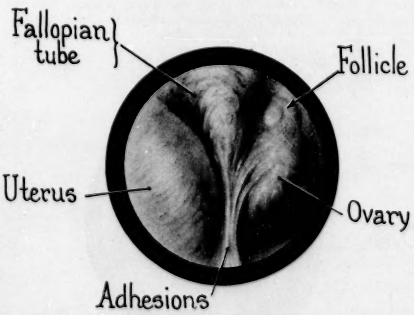


Fig. 5.—Culdoscopic view of an adherent tube and ovary.

pelvis. When it is desired to substitute carbon dioxide for air, the valve is attached to a bag containing carbon dioxide before it is opened. When the inrush of air is not heard or when the carbon dioxide is not drawn into the pelvis promptly, it is obvious that the peritoneal sac has not been entered. Failure to puncture the cul-de-sac results from improper selection of the point of puncture, loosely attached peritoneum with considerable intervening areolar or fatty tissue, or adherent struc-

3. Te Linde, R. W., and Rutledge, F.: Culdoscopy: A Useful Gynecologic Procedure, Am. J. Obst. & Gynec. **55**: 102, 1948. Rock, J., in discussion on Te Linde, p. 115.

tures within the cul-de-sac. The last two conditions can usually be apprehended before the examination by a careful pelvic examination and by a preliminary needle puncture. When some doubt is entertained concerning the ability to enter the cul-de-sac in a particular case selected for culdoscopy, preliminary puncture should be employed. On the clinic or office examining table the patient is placed in knee-chest position. The vaginal vault

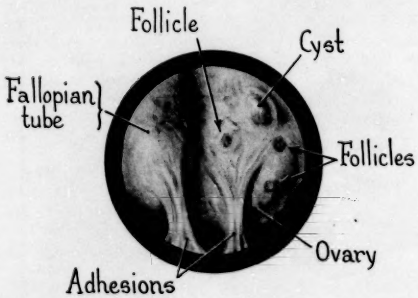


Fig. 6.—Culdoscopic view of adhesions about a cystic ovary and chronically inflamed tube.

is punctured with a 4½ inch (11 cm.) 19 gage needle attached to a 2 cc. syringe with the plunger drawn out two-thirds its length. Anesthesia is not required. When the needle point enters the peritoneal cavity the plunger of the syringe will be drawn down sharply. The needle is removed without allowing air to enter the abdomen. Inability to demonstrate intra-abdominal negative pressure by this means should usually exclude the patient from further attempts at puncture. In a few instances, when the peritoneum was loosely attached and rode ahead of the tip of the trochar, it was possible to immobilize it by means of a clamp inserted through the mucous membrane wound, while the trochar was reinserted through the same wound, or at another point for a successful puncture.

Our experience warrants the conclusion that cul-de-sac puncture for any purpose, when the pouch is not distended with fluid or blood, should be made in the knee-chest position. When a flexible cannula is used, the dorsal position may be assumed after puncture for removal of fluid, blood or cellular debris.

*Culdoscopic Visualization.*—After puncture has been accomplished and the selected type of pneumoperitoneum produced,

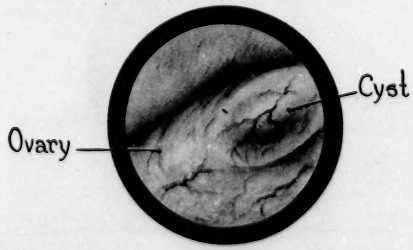


Fig. 7.—Culdoscopic view of the ovary with follicular cyst.

the trochar is removed while the cannula is held in place. The perineum may be relaxed, but the retractor kept in place. The sterile culdoscope, with dry warm lenses, is inserted into the pelvis through the cannula and locked in place. The illuminated end of the culdoscope will rarely come in contact with any structure. The nature of the septum and the construction of the cannula allow a wide range of motility of the culdoscope in every direction. It can be freely rotated so that the uterus, ovaries, tubes, broad ligaments, uterosacral ligaments, infundibulopelvic ligaments, anterior rectal wall, pelvic peritoneum, and occasionally the appendix and loops of bowel that do not fall out of the pelvis in this position, can be inspected. The viscera can be manipulated by movement of the vulsellum or by suprapubic manual pressure. The novice will require a little practice to orient himself on viewing the pelvic organs for the first time from this direction.

When detailed information concerning the tubes is desired 10 to 15 cc. of sterile indigo carmine solution may be injected through the self-retaining cervical cannula. A completely obstructed tube shows distention proximal to the point of obstruction. A partially obstructed and adherent abdominal ostium shows extravasation of the fluid under the adhesions. Patent tubes are demonstrated by the dripping of the dye from the fimbria.

When a specially designed culdoscope is employed, material for biopsy may be recovered. The contents of small cysts and follicles can be aspirated and thin adhesions interrupted. Material for smear, culture, biopsy or cytologic examination may be recovered through the puncture wound. The pelvic organs have been successfully photographed through the instrument.

*Removal of the Cannula.*—When the examination is concluded, the culdoscope is removed, but the cannula is held in

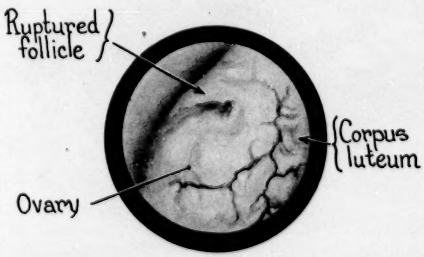


Fig. 8.—Culdoscopic view of the ovary with a recently ruptured graafian follicle.

place. A pillow is placed under the abdomen. The shoulder braces and thigh straps are removed, and the patient is allowed to lie on her abdomen on the table over the pillow. The head of the table may be lowered. The air or carbon dioxide will be heard to rush out of the abdomen, through the cannula, as the abdomen is compressed. When carbon dioxide has been introduced, little concern about removal is necessary. Oxygen is absorbed slowly, and appreciable amounts may remain for several days.

*Postexamination Care.*—The wound in the posterior vaginal vault is not sutured. Many patients walk from the table. Intraperitoneal air may give variable amounts of distress on standing, but, as in tubal insufflation, it is not prohibitive of ambulation.

The patient is instructed not to douche for one week. Assumption of the knee-chest position before the puncture is healed may result in a spontaneous pneumoperitoneum. The instrument may be reintroduced through the puncture wound before it is healed. There is no contraindication for repeated punctures.

## EXPERIENCE WITH CULDOSCOPY AND SELECTION OF CASES

In a previous report,[4] in 1946, I discussed a large group of patients examined over a period of three and one-half years. Some of the patients included

4. Decker, A.: Pelvic Culdoscopy, in Meigs, J. V., and Sturgis, S. H.: Progress in Gynecology, New York, Grune & Stratton, Inc., 1946, pp. 95-105.

in that report were examined during the time the instrument and technic were being developed.

It is the purpose of this report to relate the experience with 77 cases selected because they presented diagnostic problems that could be placed in one of four groups.

The diagnostic indications for culdoscopy may be summarized as follows:

Group A—Emergency surgical conditions, differential diagnosis of tubal pregnancy, acute appendicitis, acute salpingitis and the like.

Group B—Problem cases of long duration, when pelvic disease is suspected or cannot be excluded; e. g., pelvic tuberculosis, endometriosis, chronic pelvic inflammatory disease and neoplasms.

Group C—Menstrual disorders, such as dysmenorrhea, menometrorrhagia and amenorrhea.

Group D—Infertility study, when visualization of the tubes and ovaries is desired.

*Group A, the Emergency Surgical Group.*—These are cases in which emergency surgical treatment was being considered for suspected tubal pregnancy or appendicitis. When the symptoms and signs are atypical the differential diagnosis may be difficult.

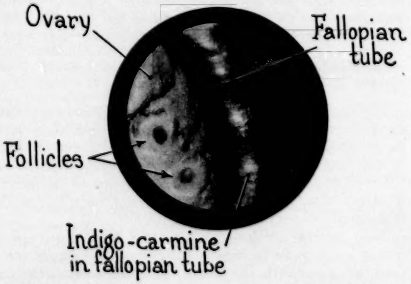


Fig. 9.—Culdoscopic view of cystic oophoritis, showing distention of the tube with indigo carmine proximal to the point of obstruction.

Prior to the employment of culdoscopy, tubal pregnancy in its atypical form accounted for a large percentage of the diagnostic errors in this category. Hemoperitoneum can usually be diagnosed by cul-de-sac needling without visualization when the needle is introduced into the rectovaginal pouch, with the patient in the knee-chest position, by the described technic.[5] Blood elements, when present, will practically always be recovered by this method. In the absence of appreciable amounts of free blood and when the history and physical observations are suggestive of atypical tubal pregnancy, culdoscopy should precede laparotomy.

Among the cases here reported, there were 11 instances when the possibility of tubal pregnancy existed and a correct diagnosis appeared desirable. The culdoscopic examination established the following diagnoses in this series: salpingitis (4 cases), early intrauterine pregnancy (1 case), cystic oophoritis (1 case), normal pelvis (1 case), tubal pregnancy (2 cases) and ruptured follicle cyst (1 case). In 1 instance the culdoscopic examination was impossible. Salpingitis was found at operation.

Atypical salpingitis may at times be difficult to differentiate from acute appendicitis without too much delay. The acutely affected tube may be readily visualized and smears or cultures may be obtained from the inflamed region.

In 10 instances the differential diagnosis was between acute appendicitis and salpingitis. In 2 such cases a normal pelvis was encountered at culdoscopic examination, so that a diagnosis of appendicitis was made in

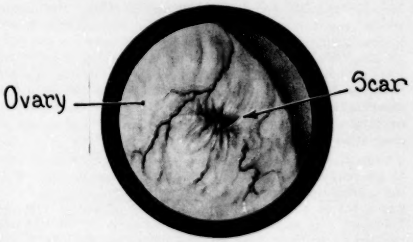


Fig. 10.—Culdoscopic view of the scar of a healing ruptured follicle.

1 case by exclusion of pelvic disease and the other by visualization of the diseased appendix. Subsequent operations verified the diagnosis in both cases.

In 6 instances tubal inflammation was the diagnosis made after cul-de-sac puncture. The puncture was unsuccessful in 2 cases.

It is a fair assumption that a few nonoperative patients in this group would have had laparotomies if a preliminary culdoscopic diagnosis had not been made. The operative diagnosis in 1 of the cases of unsuccessful puncture was salpingitis. At any rate, the diagnostic problem with few exceptions was quickly solved.

*Group B, Problem Cases of Long Duration.*—In this group lower abdominal pain and various symptoms referable to the lower part of the abdomen and pelvis occurred without demonstrable pathologic changes. They are of interest because their problems were in several instances brought to the gynecologist by the medical and surgical staff. Several cases had remained unsolved after thorough diagnostic study in the clinic and hospital and after various therapeutic measures had been tried without success. When the presumptive diagnosis was either psychoneurosis, residual pelvic

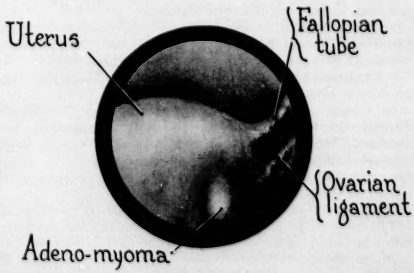


Fig. 11.—Culdoscopic view of a small adenomyoma—posterior surface of the corpus.

inflammatory disease, pelvic adhesions, early endometriosis or tuberculosis, I have frequently applied culdoscopy. The information gained has often made it

5. Decker, A.: Posterior Colpotomy for Diagnosis of Pelvic Diseases, Am. J. Surg. **73**: 313, 1947.

possible properly to evaluate the indications for or against surgical intervention.

There were 23 such cases. A brief summary of 3 cases follows.

CASE 1.—I. C., a 31 year old tripara, was admitted to the medical service on Dec. 22, 1947, with pyelitis and an enlarged spleen. After control of the urinary infection the patient had a moderately febrile course for thirty-two days before culdoscopic examination. The exact cause of the temperature, which ranged from 99 to 101 F., was not determined after thorough clinical study. Bimanual pelvic examination and pelvic pneumograms were not illuminating. Culdoscopy revealed subacutely inflamed tubes and two small intramural myomas. Sufficient pelvic fluid was obtained for guinea pig inoculation and paraffin block preparation. The fluid contained many polymorphonuclear cells but no tumor cells. Results of guinea pig inoculation were reported negative for tuberculosis.

CASE 2.—Mrs. A. M., a white bipara aged 54, was admitted to the hospital on Sept. 12, 1947, complaining of pain in the right lower quadrant of the abdomen. The onset was three weeks before admission and followed an attack of diarrhea. The pain was aggravated by her standing or walking and radiated to the right groin and suprapubic region. Twenty-four hours after admission there was pain in the right subcostal region.

The history revealed that a right radical mastectomy had been performed twelve years previously, with a pathologic diagnosis of medullary carcinoma, grade 3. Operation was followed by radiation therapy to the chest. In 1939, a right intraligamentous benign cyst was removed. In 1940, the patient was sterilized with roentgen rays for functional bleeding.

She was well nourished and did not appear acutely or chronically ill. A complete clinical study, including physical and laboratory examinations, as well as roentgenograms of the chest and gastrointestinal tract, did not permit a positive diagnosis. The right side of the diaphragm showed slight elevation and very little motility. Results of the bronchoscopic examination were normal. There was no clinical evidence of ascites.

Cul-de-sac puncture with the patient in the knee-chest position resulted in an air pneumoperitoneum and was followed by a roentgenogram of the upper part of the abdomen and the chest with the patient in the upright position. The presence of subphrenic air outlined the upper border of the liver and revealed encapsulated material above the liver. At the time of puncture about 8 cc. of fluid was aspirated from the pelvis. Paraffin block prepared from the sediment of this fluid revealed cancer cells. This diagnosis was subsequently verified by biopsy of the omentum by surgical exposure which revealed metastatic breast carcinoma.

CASE 3.—P. P., a 26 year old childless Negro housewife, was admitted by ambulance to the surgical ward on March 11, 1948, complaining of pain in the right lower quadrant of the abdomen, nausea and epigastric distress.

A similar but less severe attack had occurred one year previously. Menses began at age 14 and, except for moderate menstrual pain for one day, were regular and normal. The last menstrual period had been on February 23. There were no urinary symptoms or vaginal discharge.

In appearance, the patient was well nourished but acutely discomforted by pain in the right lower quadrant of the abdomen. The abdomen was tender in this region, with slight rebound tenderness and voluntary muscle spasm. Pelvic palpation revealed as the only abnormality some tenderness on motion of the cervix.

The temperature was 99 F., pulse rate 90, respirations 22 and blood pressure 130 systolic and 90 diastolic. Sedimentation rate was 14 mm. in one hour; hemoglobin was 11 Gm. (75 per cent), erythrocytes 3,900,000 and leukocytes 12,000, with 75 per cent polymorphonuclear cells. The urine contained no sugar or albumin, and results of microscopic examination of the sediment was not remarkable.

On the day of admission, the appendix was removed through a McBurney incision. Results of palpation of the pelvic organs at this time were reported normal. No histologic changes of significance were found in the appendix.

The postoperative course was uneventful until the sixth postoperative day. While sitting in a chair the patient had a sudden attack of severe abdominal pain with fainting. The temperature was 98.6 F., pulse rate 88 and blood pressure 120 systolic and 80 diastolic. No change of significance had occurred in the blood cell count. The lungs were clear, and the heart presented no abnormalities.

The abdomen was tender in the left lower quadrant. Thorough pelvic palpation was unsatisfactory because of acute tenderness. The uterus was normal in size and very tender on attempt at motion. There was a soft baggy painful mass (4 cm. in diameter) in the cul-de-sac. The cul-de-sac was needled in the dorsal position, and about 4 cc. of blood-stained fluid was recovered. Smear of the fluid disclosed red blood cells and many leukocytes. Staphylococcus aureus was cultured from the fluid. The diagnosis was changed from tubal pregnancy to pelvic inflammatory disease. The acute symptoms subsided.

Culdoscopic examination was advised in order further to confirm the diagnosis before the patient's discharge and because she desired an opinion as to the cause of three and one-half years of infertile marriage. Culdoscopic examination on March 25 revealed the uterus to be normal in size and position. The left ovary was normal in appearance, free from adhesions, and contained a ripening follicle. The left tube presented evidence of acute inflammation, and the fimbria was adherent to the posterior surface of the left broad ligament. The right ovary was adherent and contained a follicle cyst 3 cm. in diameter. The right tube was acutely inflamed. A loop of intestine was adherent at the brim of the pelvis on the right side. Small amounts of fluid removed contained innumerable polymorphonuclear cells and a moderate number of mononuclear cells. Culdoscopy was a distinct aid in the quick solution of this surgical problem.

My co-workers and I have, on other occasions, applied culdoscopy for indications a short time after laparotomy when it was believed that visualization at the time of operation was not complete because of the type of incision. On one occasion small endometrial implants were observed that were not included in the laparotomy observations.

Two patients in this group were examined preoperatively because there was a difference in opinion concerning the exact diagnosis and the advisability of operation. An ovarian cyst was visualized in one, and in the other chronically thickened and adherent tubes. The culdoscopic diagnoses were confirmed at surgical exposure.

Another patient had an undiagnosed febrile hospital course of thirty-eight days on the medical service before culdoscopy was employed. Unsuspected serosal tubercles of the bowels were visualized. The pelvic organs were normal. No previous evidence of tuberculosis had been obtained. The diagnosis was subsequently further confirmed by positive microscopic observations in cervical glands.

Three patients treated in the hospital for acute pelvic inflammatory disease were examined by culdoscopy before discharge to the clinic. These were patients in whom persistent symptoms or signs created a suspicion of tuberculosis, endometriosis and cystoma. These conditions were ruled out in each instance.

The puncture was unsuccessful in 1 instance. In the remaining cases of this problem group, the visual diagnosis was a valuable aid in the selection of the proper therapy.

Functional disturbance of the nervous system with symptoms referable to the pelvis is a common problem that confronts the gynecologist with increasing frequency. One cannot arrive at a conscientious diagnosis of psychosomatic disease without positively excluding actual disease. It is possible that this group accounts for a large percentage of the unnecessary elective opera-

tions and exploratory laparotomy. Our experience leads us to believe that mistakes are also made in the other direction, and the patient with a real but nonpalpable pathologic condition is at times classified as neurotic.

In 4 such cases, culdoscopic visualization warranted the removal of the patient from the surgical to the psychosomatic group. Three patients had been considered psychosomatic after a long period of clinic attendance. Culdoscopic visualization demonstrated pelvic inflammatory disease and adhesions in amounts sufficient to account for the symptoms in 2 cases. Endometriosis was the visual diagnosis in the third patient.

*Group C, Menstrual Disorders.*—In this group the symptoms were amenorrhea, dysmenorrhea or other previously unexplained menstrual abnormalities. Seventeen cases comprise this group. The symptoms were present in nearly all cases for a long time. Many of the patients had been subjected to various diagnostic procedures and had received therapy of several types for extended periods without relief of the symptoms. The following case is illustrative.

CASE 4.—G. C., a 31 year old English war bride, sought relief in December 1947 for primary amenorrhea and sterility. There were no other complaints. This 128 pound (58 Kg.) white woman was well nourished and apparently in excellent health and regularly employed as a secretary. She had until recently engaged in competitive swimming events. There was no physical evidence of endocrine disturbance. Endocrine therapy of various types had been employed for several years. The most frequent previous diagnosis had been endocrine amenorrhea, primarily ovarian.

The results of the physical examination were essentially normal. Roentgenograms of the chest and pituitary did not reveal any evidence of disease. The endometrial biopsy diagnosis was atrophic endometrium. There was no evidence of extensive pelvic disease. A cystic mass, 3 cm. in diameter, was palpable in the left ovarian region.

On culdoscopic examination, a grayish white area, 1.5 cm. in diameter and slightly elevated, was observed on the uterine serosa at the fundus. The right tube was thickened and fixed and presented two small serosal tubercles. There was a serosal cyst 3 cm. in diameter on the posterior surface of the left broad ligament. The ovaries appeared white and sclerotic. There was no evidence of follicular activity. The culdoscopic diagnosis of pelvic tuberculosis was confirmed at operation.

There were 3 cases of severe dysmenorrhea. The condition in 1 was primary and in 2 acquired. Their problems were unsolved after thorough clinical study and extensive trial of therapeutic measures by several gynecologists. The culdoscopic diagnoses in these cases were: adenomyosis of the uterus, endometriosis of the ovary and chronic salpingitis. The diagnosis was confirmed in each instance by laparotomy. Abnormal menstrual bleeding was present in 3 other cases, brief descriptions of which follow.

CASE 5.—There was postmenopausal bleeding in a 62 year old white woman. Curettage was done on two occasions, at eight month intervals, and the diagnosis was hyperplastic endometrium. An ovarian tumor was suspected but was not palpated. Culdoscopic visualization disclosed the left ovary transformed into a solid white smooth surface tumor 3 cm. in diameter. Laparotomy confirmed the culdoscopic impression of granulosa cell tumor.

CASE 6.—A white multipara, aged 32 years, had irregular menstrual flow lasting from five to as many as forty days during the three years prior to examination. This complaint was unrelieved after extensive diagnostic and therapeutic measures. She was admitted to the hospital for removal of a cystic ovary. Culdoscopic examination revealed a normal pelvis without evidence of disease.

CASE 7.—A 25 year old married housewife had lower abdominal pain in recurring attacks for fourteen months. She experienced severe dysmenorrhea and irregular bleeding. This was the second hospital admission in less than a year. The diagnosis at discharge eight months previously was acute pelvic inflammatory disease, and the patient was referred to the clinic for treatment. Regular clinic attendance for eight months did not result in relief. She was again referred to the ward for surgical treatment with the diagnosis of tubo-ovarian disease. Culdoscopic examination after admission revealed an entirely normal pelvis with normal-appearing tubes and ovaries. She was not operated on.

Nine patients (aged 23 to 28) had as their chief complaint abnormal bleeding with irregular intervals and increase in duration of the flow. Variable amounts of menstrual pain were also present. In each instance the symptoms had been of several months' duration and the exact cause was not determined. Salpingitis with adhesions was the unsuspected diagnosis in 2 instances. In 2 cases the pelvic organs were normal in appearance. In 3 cases the presence of suspected pelvic inflammatory disease was confirmed, and the exact extent of the disease noted. Two punctures were unsuccessful.

*Group D, Infertility Problems.*—The cases that I choose to report here were examined after long periods of infertile mating. The routine investigations were made previous to culdoscopic visualization by competent investigators.

In 16 instances, the visualization was for the purpose of answering one of two questions. Is this particular pelvis entirely free of disease as the routine investigators indicated? If so, what is the functional appearance of the ovaries? In the second instance, the problem has been presented as follows. There is evidence of pelvic disease—tubal, ovarian or uterine. Can the actual extent and location of the disease be determined in detail so that a more conscientious opinion can be given concerning further therapy or the chances for surgical relief?

In 13 cases I was able to answer that question in detail, in the more recent cases by photographs in color. I have found disease when the pelvis was believed to be free from disease. Adhesions causing various types of derangement of the ovarian tubal relations have been disclosed when the investigation before culdoscopic examination indicated more extensive disease. Endometriosis was visualized in 2 cases in this group. In 1 instance it was an unsuspected observation.

In 3 cases puncture was unsuccessful—visualization was not possible. In another group of cases of sterility there was a large percentage of failures, so that at present, in order to avoid the unnecessary preparation for the procedure, I resort to preliminary needle puncture, before arranging for culdoscopic examination.

## COMMENT

Pelvic pain, menstrual irregularities and dysmenorrhea, as well as sterility, may be produced by many types of pelvic lesions that are not readily palpable. Frequently their presence is suggested by the history, but occasionally such evidence is absent or misleading.

Endometriosis is a frequent cause of these complaints. The severity of the pain may not bear any relation to the extent of the disease. Endometriosis can be seen before it can be felt. The appearance is distinctive and would rarely be confused with other pathologic changes. Arrest of this disease in young women without castration requires a diagnosis while the disease is still resectable. I have recognized these small lesions on the peritoneum, broad ligament, uterus and ovary on several occasions during culdoscopic examination. Fal-

lon[6] has aptly stated that to the eye endometriosis is as unmistakable as chickenpox.

When tuberculosis appears as serosal tubercles on the uterus, tubes, bowel or peritoneum, it also presents a distinctive appearance. One may also recognize caseous material as it exudes from the fimbrial end of a thickened tube. The recognition by culdoscopic visualization of this condition when neisserian infection or endometriosis is suspected is particularly gratifying.

Many gynecologists have experienced the chagrin that results from failure to diagnose tubal pregnancy after employing all the usual diagnostic methods. The visual diagnosis is distinctive and readily obtained.

The exploratory laparotomy has a definite place in pelvic surgery. Some critics are of the opinion that pelvic organs containing only a minimal amount of disease are too frequently removed when surgically exposed. Diagnosis by culdoscopy in such cases frequently permits further deliberation to temper the judgment.

## SUMMARY AND CONCLUSION

With the patient in the knee-chest position, the rectovaginal pouch may be punctured by needle or trochar by a technic that is simple and safe. Endoscopic visualization of the female pelvis was attempted in 77 cases, when the diagnosis made by other means was indefinite or doubtful. The examination was successful and of diagnostic value in 88.3 per cent of the cases selected. The puncture was unsuccessful in 9, or 11.7 per cent, of the cases. When the puncture was possible, detailed information was obtained concerning the pelvic disease present.

The procedure was particularly useful in disclosing 2 cases of tuberculosis, 4 cases of endometriosis and 1 each of adenomyosis and ovarian neoplasm.

The culdoscopic diagnosis was verified at operation or by subsequent events in all cases. On occasions exploratory laparotomy in suspected surgical emergencies was avoided. A more prompt diagnosis has in some instances resulted in reduction of days of hospitalization and in the number of clinic visits. The procedure has been useful in the solution of problems of menstrual abnormality. In 13 selected infertility problems detailed information was gained concerning the condition of the tubes and ovaries.

There were no serious complications or accidents in these cases. Culdoscopic visualization is a useful and harmless diagnostic procedure that allows a prompt and positive diagnosis in a large variety of gynecologic problems not readily diagnosed by the usual methods.

## ABSTRACT OF DISCUSSION

DR. R. W. TE LINDE, Baltimore: It was Dr. Decker's cleverness in seeing the advantage of the knee-chest posture that has made culdoscopy a successful and practical procedure. My co-workers and I have been interested in visualization of the pelvic organs, and we used extensively the ordinary transabdominal peritoneoscopic approach. We found it useful, but not nearly as useful or practical as culdoscopic visualization. I attempted culdoscopic examination with the ordinary peritoneoscope with the patient in the lithotomy position. I was unsuccessful because the crowding of the intestines about the end of the peritoneoscope. Decker overcame this by the use of the knee-chest posture, and, using his technic, we have employed culdoscopic examination in 85 women in our clinic in the past two years. Culdoscopy has several advantages over transperitoneal peritoneoscopy. In ordinary peritoneoscopic examination one has to transverse many loops of bowel to get to the pelvis. These loops of bowel may be troublesome. In peritoneoscopy one must pump air into the peritoneal cavity. In culdoscopy air rushes in spontaneously. In peritoneoscopy one runs the risk of contaminating the peritoneal cavity on withdrawal of the peritoneoscope if pus is encountered in the pelvis. In culdoscopy no harm is done if one encounters pus, and even drainage may be derived from the cul-de-sac puncture. In peritoneoscopy abdominal adhesions may prevent the end of the peritoneoscope from reaching the pelvis. Cul-de-sac adhesions and tumor occupying the cul-de-sac are the only mechanical contraindications to culdoscopy, and careful pelvic examination will usually detect these before culdescopy visualization is attempted. Our indications for culdoscopy have corresponded with those of Dr. Decker. We have used it oftenest in cases of suspected tubal pregnancy, and we have no reason to suspect that the information obtained by culdoscopy has been fallacious. One of the most constant sources of worry to the gynecologist is the slight ovarian enlargement which may be due to a retention cyst, which does not require removal, and a neoplastic cyst or tumor, which does. Culdoscopic visualization usually enables one to decide this promptly. Concerning the woman with pelvic symptoms and normal or minimal observations on pelvic examination, is she to be treated for organic pelvic disease or on a psychosomatic basis? Mistakes are made in both directions, but fewer will be made if the culdoscope is used to visualize the organs. There is one point in technic that I want to emphasize. In his fear of injuring the rectum the novice is apt to puncture too close to the cervix, dissect up the peritoneum as it is reflected onto the cervix and thus fail to enter the peritoneal cavity. The thinnest point of the septum is usually 2 to 3 cm. from the reflexion of the vaginal mucosa onto the cervix. The rectum has been punctured only once on our service. This puncture was extraperitoneal and healed spontaneously without even temperature elevation.

DR. W. D. BEACHAM, New Orleans: I agree with Dr. Decker that in suspected hemoperitoneum, cul-de-sac aspiration is a valuable diagnostic procedure. I ordinarily place the patient in a dorsal position. Needling of the cul-de-sac with the patient in the knee-chest posture should be performed prior to attempted culdoscopic visualization in cases in which the advisability of endoscopic examination through the rectovaginal pouch is doubtful. I have not found it necessary to employ culdoscopic examination in patients for whom the diagnosis was narrowed down to appendicitis or ectopic pregnancy. Also, I do not deem it advisable in the differentiation of acute salpingitis from acute appendicitis. Group B cases, as pointed out by Dr. Decker, form the largest category in which culdoscopy is most useful. In these cases one may gain information which makes it possible to evaluate the indications for or against operation. Next in my experience are cases in classification D. The essayist has been overmodest in mentioning the simplicity of this procedure. However, even in his expert hands the puncture was unsuccessful in 11 per cent of his cases. My co-workers and I have investigated the subjects of analgesia and position. In some nulliparous patients we have resorted to preoperative medication, consisting of seconal® sodium (sodium 5-allyl-5-[1-methylbutyl] barbiturate, meperidine hydrochloride and scopolamine, and employed pudendal block and local infiltration anesthesia. Now we are checking on the feasibility of intrathecal anesthesia. In our more recent cases we have used a position which requires an operating room table with a kidney elevator. With the patient well sedated we place her in a dorsal lithotomy position, aseptically catheterize the urinary bladder and then thoroughly prepare the vulva and vagina with soap and water followed by the application of benzalkonium chloride or merthiolate® solution (sodium ethylmercurithiosalicylate). The patient is then turned over into a prone posture. With her thighs resting on the kidney elevator the anterior abdominal wall hangs in such a manner as to cause the required negative pressure for easy local anesthetization of the area to be punctured and for good visualization with the culdoscope. Even though the patient is well analgized, thigh straps and leg holders are not needed. The table alone supports her. This position is easy on both patient and culdoscopist.

6. Fallon, J.; Brosnan, J. T., and Moran, W. G.: Endometriosis: Two Hundred Cases Considered from Viewpoint of the Practitioner, New England J. Med. **235**: 669, 1946.

DR. IRVING F. STEIN, Chicago: At Michael Reese Hospital, Chicago, we have employed gynecography for pelvic diagnosis in the past twenty-five years, in preference to culdoscopy. As in culdoscopy, pneumoperitoneum is utilized; however, we rely on visualization on the roentgenogram for diagnosis. All of the evidence which can be obtained by culdoscopic visualization can likewise be recorded on the roentgenogram except for color of the organs. Gynecography is a far less formidable procedure and is of particular value for consultation purposes. Unlike culdoscopy, in which only the examiner interprets the observations, pneumoperitoneum presents a permanent record which is available for numerous opinions.

DR. ALBERT DECKER, New York: It is gratifying to hear that others have found culdoscopy valuable. I want to thank Dr. Te Linde and Dr. Beacham for their discussion and for their contribution to this subject. I have been asked the reason for the unsuccessful punctures among the cases reported. Puncture cannot be accomplished in all cases. This is either because of loose attachment of the peritoneum, so that it rides ahead of the trochar, or because of the presence of a pelvic mass or adhesions. It is my practice to make a preliminary puncture in the office or clinic in doubtful cases. If I can measure intra-abdominal negative pressure with a small needle, I am certain that the pelvis can be punctured with the trochar.

## NEEDLE BIOPSY OF THE LIVER

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During the past four years needle biopsy of the liver has been carried out at the Cincinnati General Hospital 403 times on 345 patients. There has been no fatality or hemorrhage severe enough to require blood transfusion. In 1947, we reported experiences with 195 biopsies made on 170 patients.[1] The present report serves to describe our experience to date, since, during the past year, 208 additional biopsies have been performed on 175 patients.

The patient is prepared for the procedure by the administration of 50 to 100 mg. of meperidine hydrochloride N. N. R. (demerol®) hypodermically approximately one-half hour before the biopsy.[2] A liver extending 5 cm. or more below the right costal margin may be approached anteriorly or transpleurally. A smaller liver is approached transpleurally in the right anterior or midaxillary line. In our group of patients, the transpleural route was used 328 times and the anterior approach, 75 times.

### METHOD

In the transpleural method the upper limit of liver dulness is suitably marked during ordinary respiration, usually in the anterior axillary line. The area chosen is sterilized with iodine tincture U. S. P. and alcohol and draped with sterile towels. The operator wears sterile rubber gloves. The skin, subcutaneous tissue, intercostal muscle, pleura, diaphragm, Glisson's capsule and hepatic substance are infiltrated with 2 per cent procaine hydrochloride solution, care being taken to penetrate beyond the intercostal space only while the patient is holding his breath at the end of full expiration. Approximately 8 cc. of procaine hydrochloride solution is used. A small incision is made in the skin over the procaine bleb with a no. 11 Bard-Parker blade to permit easy entry of the biopsy needle. The Vim-Silverman needle [3] is introduced into the incision, with the forked obturator inserted in such a position that its tip is just visible at the distal end of the carrier needle. Then, after the patient inhales and exhales deeply two or three times, he is instructed to hold his breath at the end of expiration and the needle assembly, in the position described previously, is inserted a distance of approximately 6 cm. (2 to 3 cm. into the substance of the liver). The obturator is then pushed firmly the final 2.5 cm. into the needle, while the latter is held steady, after which the obturator tip is held steady while the carrier needle is advanced over the obturator, bringing the assembly back to its original relations, but advanced 2.5 cm. farther into the liver. This cores a fragment of hepatic tissue 1 to 2 mm. in diameter and 1 to 2 cm. in length and grasps it tightly in the obturator fork. The entire assembly is rotated approximately 120 degrees, breaking the terminal attachments of the fragment to the liver, and is then withdrawn from the patient. (The average time elapsing between entry of the Vim-Silverman needle into the substance of the liver and its removal is five to ten seconds.) A simple dressing is applied, and the patient is instructed to remain quietly in bed for twenty-four hours. A synthetic vitamin K preparation, 10 mg., is administered parenterally immediately after the biopsy is accomplished, and codeine is used to control any postbiopsy pain. One half of the biopsy specimen is fixed in a 10 per cent solution of formaldehyde U. S. P. (formalin®); the other half is fixed in acetone for special stains. As described in a previous paper,[1] if hepatic tissue is not obtained on the first attempt, additional attempts are made at the same site. This practice has decidedly reduced the number of failures and has resulted in no demonstrable harm to the patient.

### INDICATIONS

The following are considered proper indications for needle biopsy of the liver:

1. Hepatomegaly of undetermined cause.

2. Need for distinction between parenchymal and extrahepatic obstructive jaundice. The changes characteristic of infectious hepatitis, the most frequent form of parenchymal jaundice, were well described by Dible, McMichael and Sherlock [4] and by Mallory,[5] and those of obstructive jaundice by Roholm and Krarup,[6] Popper and Franklin [7] and McMichael.[8]

3. Primary or metastatic neoplasm of the liver. Our experiences with cases of neoplasm of the liver will be published elsewhere.[9] In this entire study, primary or secondary neoplasm of the liver was demonstrable by means of needle biopsy in 41 of 53 cases. In the case of an enlarged and nodular liver, it is theoretically desirable to insert the needle anteriorly into a nodule.

The study was aided by a grant from the Henry Meiss Fund.

Dr. Cogswell, Dr. Safdi, Dr. Richfield and Dr. Kumpe were Fellows of the National Cancer Institute, 1947 and 1948.

Dr. W. E. Molle and Dr. H. H. Steinberg performed some of the biopsies and Dr. Ben Friedman compiled some of the data included in this report.

From the Departments of Internal Medicine and Pathology, College of Medicine, University of Cincinnati, and the Gastric Laboratory of the Cincinnati General Hospital.

Read in part before the Section on Gastroenterology and Proctology at the Ninety-Seventh Annual Session of the American Medical Association, Chicago, June 23, 1948.

1. Kumpe, C. W.; Gall, E. A.; Schiff, L.; Molle, W. E.; Safdi, S. A., and Steinberg, H. H.: Needle Biopsy of the Liver: I. General Considerations, Gastroenterology **9**: 672, 1947.

2. We have been carrying out this practice as advocated by Volwiler and Jones (The Diagnostic and Therapeutic Value of Liver Biopsies with Particular Reference to Trochar Biopsy, New England J. Med. **237**: 651, 1947) since January 1948. Prior to that time, no sedative was given before biopsy.

3. Manufactured by the MacGregor Instrument Co., Needham, Mass.

4. Dible, J. H.; McMichael, J., and Sherlock, S.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic Arsenotherapy and Serum Jaundice, Lancet **2**: 402, 1943.

5. Mallory, T. B.: Pathology of Epidemic Hepatitis, J. A. M. A. **134**: 655 (June 21) 1947.

6. Roholm, K., and Krarup, N. B.: Histopathology of the Liver in Obstructive Jaundice, Examined by Aspiration Biopsy, Acta med. Scandinav. **108**: 48, 1941.

7. Popper, H., and Franklin, M.: Diagnosis of Hepatitis by Histologic and Functional Laboratory Methods, J. A. M. A. **137**: 230 (May 15) 1948.

8. McMichael, J.: Disease of the Liver: A Review of Some Clinical and Biochemical Problems as Reviewed by Systematic Biopsy Studies, J. A. M. A. **137**: 234 (May 15) 1948.

9. Safdi, S. A.; Gall, E. A.; Kumpe, C. W., and Schiff, L.: Needle Biopsy of the Liver: II. Experience with Malignant Neoplasm, Gastroenterology **11**: 93 (July) 1948.

4. Hepatic cirrhosis. The type of cirrhosis present may be elucidated by liver biopsy. Rarely, a nodule of hyperplasia may be entered by the needle, in which case the increased fibrosis and other structural abnormalities characteristic of cirrhosis may be missed. Because of the fibrosis, it is somewhat more difficult to take biopsy specimens of cirrhotic livers than of those which are the site of hepatitis or neoplasm. In the presence of ascites, it is necessary to drain off as much ascitic fluid as possible in order to keep the liver from floating away from the needle.

5. Determination of progress of hepatitis. Biopsy is of particular value in patients with minimal or equivocal laboratory evidence of hepatic damage or in those with the "posthepatitis syndrome."[10]

6. Evaluation of therapy. In certain instances of hepatic disease, histologic improvement may occur in the absence of corresponding improvement in the results of laboratory tests or vice versa. Microscopic examination of serial biopsy specimens in these cases may demonstrate correction of the cytologic or structural derangement following treatment. In fatty infiltration of the liver, diminution in the extent of the lesions may be demonstrated in the absence of demonstrable laboratory or clinical change.

7. Unrecognized systemic disease. Pathologic changes in the liver may be demonstrated in many diseases in the absence of signs of hepatic involvement. The lesions, when correlated with other clinical and laboratory findings, may make the diagnosis clear. Included among such diseases are miliary tuberculosis, brucellosis, sarcoidosis and infectious mononucleosis.

## CONTRAINDICATIONS

Although the contraindications to needle biopsy of the liver are few, the following represent those to which we have adhered:

1. Uncooperative patient. As emphasized by Sherlock,[11] the uncooperative patient is not a suitable candidate for this procedure, since a certain ability and willingness to follow instructions is essential to success. This statement should be construed to include stuporous and comatose patients, as well as children, unless the anterior subcostal approach can be used.

2. A low blood prothrombin content or other evidences of aberrations in the coagulating mechanism. These indicate a real danger of hemorrhage. We have taken a prothrombin concentration of 50 per cent of normal (Quick method) as the minimum below which a biopsy should not be done. As recorded previously, no hemorrhage sufficient to require blood transfusion has occurred in more than 400 biopsies.

3. Infection in the lower lobe of the right lung or right pleural cavity. Biopsy during such infection is inadvisable, because of the possibility of spread to contiguous structures, including the liver.

4. Ascites. Because ascites permits some degree of mobility of the liver, it increases the difficulty of obtaining a satisfactory biopsy specimen, especially in the presence of cirrhosis. For this reason, an abdominal paracentesis should be done before the biopsy is made. Some of the failures to obtain satisfactory specimens in the present series resulted from failure either to observe this precaution or to remove sufficient ascitic fluid at the time of paracentesis.

5. Chronic passive congestion of the liver. Some observers have not hesitated to take a biopsy specimen from a liver congested with blood as the result of cardiac failure. Inasmuch as it would seem that the increased vascular engorgement would make the risk of hemorrhage considerably greater, we have empirically included this condition as a contraindication.

## REACTIONS

We have observed the following types of reaction, none of which has proved to be serious:

1. Pain at the site of entry with radiation to the right shoulder. This occurs at the time the biopsy is performed. It is mild and transient and has been noticed by approximately 30 per cent of the patients. A similar reaction occurring after the local anesthesia has dissipated has been observed in a somewhat higher proportion of the patients. This is readily counteracted with codeine and acetylsalicylic acid. It rarely lasts longer than twelve hours and presumably results from local trauma and diaphragmatic irritation.

2. Epigastric discomfort or pain. This is experienced during the time the needle assembly is within the hepatic substance. It is moderately severe on occasion and should be anticipated, since the patient may take a sudden breath if not previously warned.

3. Friction rub. Developing in the region of the biopsy site, this is probably due to fibrinous perihepatitis. The rub is usually of short duration, but in 1 case it persisted for several weeks.

4. Intra-abdominal hemorrhage. This represents the most feared complication, since it was the principal cause of the disasters which have occurred in other series. To date, no serious postbiopsy hemorrhage has been observed in our patients. Close observance for evidences of bleeding should be maintained for twenty-four to forty-eight hours following the biopsy. Blood transfusions may be necessary, and, in the event the hemorrhage continues, operative intervention may be required.

5. Hemorrhage into the pleural cavity or pleural effusion. Penetration of an intercostal vessel or injury to the pleura at the time of penetration may result in hemothorax or transitory pleuritis. Although an effusion was initially attributed to the biopsy in 1 patient in our group, examination at autopsy demonstrated the presence of bilateral effusion resulting from other causes. Injury to the intercostal vessels can be avoided by keeping the needle close to the rib bounding the lower margin of the interspace.

6. Pneumothorax. This was observed in 2 patients. In 1 instance a blunt scalpel blade used in making the incision through the skin penetrated the parietal pleura. The other was associated with pronounced edema of the wall of the chest. In neither instance did the associated pulmonary collapse exceed 10 per cent, nor were there other than mild symptoms.

7. Severe apprehension associated with various nervous and hysterical manifestations. In 1 patient with auricular fibrillation, extreme agitation and impending syncope were observed. There was also an increase in pulse rate. Another patient, who was both agitated and depressed at the prospect of biopsy, developed what appeared to be hysterical apnea lasting approximately ninety seconds. During the apneic period, the pulse rate increased only slightly, blood pressure was maintained and no cardiac lesion could be demonstrated

10. Sherlock, S., and Walshe, V.: Post-Hepatitis Syndrome, Lancet 2:482, 1946.
11. Sherlock, S.: Aspiration Liver Biopsy: Technique and Diagnostic Application, Lancet 2:397, 1945.

later. The patient had amnesia for this period but showed no ill effects.

It should be emphasized, in perusing this list of observed reactions that the majority of patients suffer little or no abnormal response. Although they cannot be said to be eager to have repeated studies, patients do not refuse subsequent biopsies.

Fig. 1 (patient G. C.).—Infectious hepatitis (low power). There is loss of lobular structure with "ballooning" of polygonal cells and focal cellular disintegration evidenced by stromal collapse and lymphocytic clusters. Occasional binucleated cells may be seen.

## VALUE OF LIVER BIOPSY

Under the categories listed as indication for liver biopsy, the following cases have been selected to demonstrate the value of the procedure:

*Evaluation of Presumptive Hepatomegaly.*—R. C. was a well developed, well nourished 8 year old white girl who was found, five months previously, to have hepatomegaly without evident cause or complaint. Four of 5 siblings presented a similar finding. The results of hepatic function tests on all 5 were normal, but 2 of the 5 siblings and the patient had positive reactions to skin tests with histoplasmin. Physical examination revealed slight lymphadenopathy. The liver was palpable 1½ fingerbreadths below the right costal margin. It was smooth, soft and nontender. Results of thymol turbidity, thymol flocculation, cephalin-cholesterol flocculation and serum bilirubin tests were all within normal limits. As no diagnostic abnormalities were recognized in the biopsy specimen, we dismissed the probability of hepatic disease. Our experience with liver biopsy in general has convinced us of the frequency with which a normal liver may be palpable 1 to 2 fingerbreadths below the right costal margin.

*Differential Diagnosis of Jaundice.*—G. C., a 63 year old white man, was admitted to another hospital because of jaundice. He had had a subtotal gastrectomy five and one-half months previously for gastric ulcer. At the time of operation he received one blood transfusion. One week before his present admission, he noted frontal headache, a "jittery feeling" and dark urine. The following day he observed yellow discoloration of his skin and eyes. Two days before admission diarrhea developed, the stools being whitish. On physical examination, the liver was found to extend 4 fingerbreadths below the right costal margin. It was soft and nontender, save for a tender nodule on the inferior border in the midclavicular line. Dependent edema (1 plus) was noted. Thymol turbidity of 1 unit was observed, with 3 plus cephalin-cholesterol flocculation in twenty-four and forty-eight hours. Serum alkaline phosphatase measured 13.2 Bodansky units per hundred cubic centimeters. Because of the patient's age, the tender nodule and the increased serum alkaline phosphatase, a diagnosis of jaundice due to neoplasm was made by his physican and the patient was scheduled for exploratory laparotomy. A liver biopsy (fig. 1) revealed the presence of subacute hepatitis, thus averting an unnecessary operation.

H. S., a 54 year old Negro man, was admitted to the hospital with jaundice and an eighteen month history of weakness, intermittent abdominal pain and loss of weight of undetermined amount. The pain had become worse two weeks before admission. Acholic stools and dark urine were said to have been present for one week, and vomiting for three days. The abdomen was slightly distended. The liver extended 5 fingerbreadths below the right costal margin. The gallbladder was not palpable on admission. Thymol turbidity was 2 units. The thymol flocculation test gave negative results. Cephalin-cholesterol flocculation was normal in twenty-four to forty-eight hours; serum alkaline phosphatase was 20.8 Bodansky units per hundred cubic centimeters. Serum bilirubin measured 11.5 mg. prompt and 17.3 mg. total per hundred cubic centimeters. The liver biopsy revealed pronounced bile stasis and acute cholangitis (fig. 2). At operation, a carcinoma of the ampulla of Vater was found. There was no hepatic metastasis.

*Diagnosis of Neoplasm of the Liver.*—A. R., a 39 year old white woman with a known gastric ulcer, had experienced weakness and fatigue for two weeks before her admission. There were generalized aches and pains with headache, dark urine and moderate pain in the right upper quadrant of the abdomen. For ten years the patient had had intolerance to fatty foods, with bouts of nausea, vomiting and abdominal pain radiating about both costal margins. Jaundice was present. The liver extended 4 fingerbreadths below the right costal margin and was firm and tender. The gallbladder and spleen were not palpable. Thymol turbidity was 2 units. Cephalin-cholesterol flocculation was negative in twenty-four and forty-eight hours. Serum alkaline phosphatase measured 3.4 Bodansky

Fig. 2 (patient H. S.).—Bile stasis (high power). An area adjacent to a central vein showing a large plug of inspissated bile filling an intercellular canal. Polygonal cells here are essentially normal in appearance.

units per hundred cubic centimeters. On the prompt reaction serum bilirubin was 10 mg. and the total reaction was 12 mg. per hundred cubic centimeters. The patient was thought by some examiners to have infectious hepatitis, possibly of the cholangiolitic type, with antecedent gallbladder disease. In the opinion of others she had a stone in the common duct. Liver biopsy revealed metastatic adenocarcinoma, the primary site of which was not determined.

On occasion one may anticipate considerable difficulty in confirming the presence of hepatic tumor by liver biopsy when the clinical diagnosis appears obvious. In 1 patient with a large nodular liver, the transpleural biopsy specimen showed nothing abnormal. A subsequent needle biopsy was made over a nodule through the anterior subcostal approach. Although four pieces of tissue were removed, evidence of hepatoma was seen in only a small area of one of these fragments.

*Determination of the Degree of Progress and the Extent of Hepatic Damage in Cirrhosis.*—J. H., a 47 year old white man who had chronic alcoholism, was admitted to the Cincinnati General Hospital in 1942 with hematemesis and ascites. A

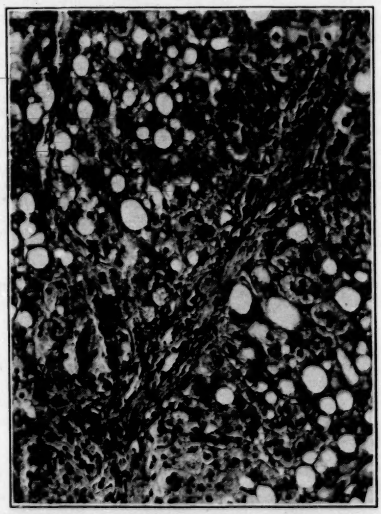

Fig. 3 (patient J. H.).—Nutritional deficiency cirrhosis (low power). Lobular structure is distorted by narrow, relatively acellular strands of connective tissue. Parenchyma exhibits heavy fatty vacuolization with occasional individual cellular degeneration.

large liver and dilatation of the veins of the abdominal wall were observed. Following his discharge from the hospital, he remained indifferently temperate until two and one-half months prior to his admission in 1947, when he indulged in a prolonged drinking spree, neglecting the while to consume adequate food. Eight days prior to his admission dependent edema and abdominal swelling developed, for which he finally came to the hospital. Physical examination revealed the presence of pectoral alopecia, slight icterus, palmar erythema, numerous spider telangiectases and moderate ascites. The liver was palpated at the level of the umbilicus. Thymol turbidity measured 2 units; thymol flocculation was normal. The cephalin-cholesterol flocculation test showed a 3 plus reaction in twenty-four hours and a 4 plus reaction in forty-eight hours. Serum bilirubin was 1.5 mg. on direct reaction and 2.5 mg. per hundred cubic centimeters on total reaction. Bromsulfalein retention was 29 per cent in forty-five minutes. Three liver biopsies (fig. 4) in a period of seven weeks demonstrated the presence of micronodular cirrhosis, heavy lymphocytic infiltration and fatty vacuolization. The amount of fatty vacuolization was seen to decrease progressively with a hospital diet and rest in bed.

*Progress of Hepatitis.*—J. D., a 14 year old white girl, experienced fatigue, anorexia and mild nausea ten days before

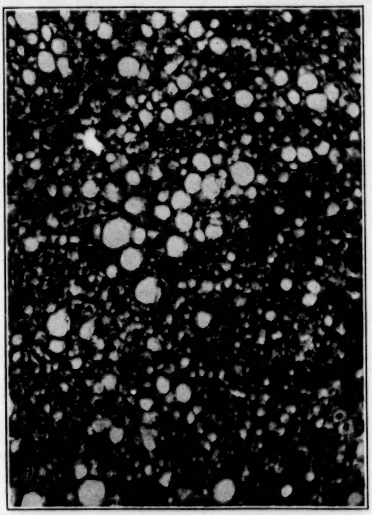

Fig. 4 (patient J. M.).—Fatty infiltration before therapy (low power). The section shows a massive coarse, fatty vacuolization of the parenchyma.

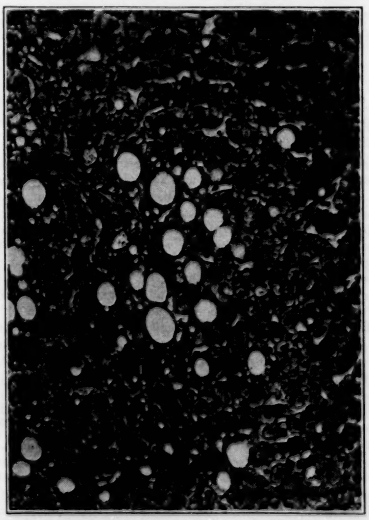

Fig. 5 (patient J. M.).—Fatty infiltration after therapy (low power). Repeat biopsy after ten months of therapy demonstrates notable diminution of the fatty infiltration.

admission. Icteric scleras and mild, dull pain in the epigastric region and right upper quadrant appeared one week before

her admission. Clay-colored stools and dark urine were noted for three days. Physical examination demonstrated the presence of icterus and spider telangiectases. The liver was just palpable below the right costal margin and was tender to both palpation and fist percussion. Thymol turbidity was 12 units; the thymol flocculation test showed a 4 plus reaction. Cephalin-cholesterol flocculation was 3 plus in twenty-four and forty-eight hours. Serum alkaline phosphatase measured 11.6 Bodansky units per hundred cubic centimeters. The first biopsy specimen taken showed little cellular damage, save in the vicinity of the central veins, where a scant lymphocytic reaction obtained. Inflammation of portal islets was particularly prominent, and there was moderate bile stasis confined to the periphery of the lobules. A second biopsy specimen obtained two weeks later revealed the parenchyma to be in the main intact with no bile stasis, in contradistinction to the previous specimen. The portal islets revealed pericholangitis of moderate severity, and in the region of the central vein some disintegration of the hepatic cells was associated with a lymphocytic infiltrate. The third biopsy specimen, procured seven weeks after the onset of the illness, revealed no recognizable abnormality of the hepatic parenchyma. Several portal islets were widened and showed persistence of moderate chronic inflammatory infiltrate. The

TABLE 1.—*Changes in Clinicol Diagnosis as a Result of Liver Biopsy (51 Cases)*

| No. of Cases | Clinical Diagnosis | No. of Cases | Diagnosis on Biopsy |
|---|---|---|---|
| 14 | Acute hepatitis | 6 | Cirrhosis |
| | | 4 | Obstructive jaundice |
| | | 1 | Fatty vacuolization |
| | | 1 | Intracellular bile stasis |
| | | 1 | Metastatic adenocarcinoma |
| | | 1 | Normal liver |
| 17 | Portal cirrhosis | 5 | Fatty vacuolization |
| | | 4 | Normal liver |
| | | 3 | Metastatic adenocarcinoma |
| | | 2 | Obstructive jaundice |
| | | 1 | Biliary cirrhosis |
| | | 1 | Hepatoma |
| | | 1 | Alcoholic hepatitis |
| 4 | Obstructive jaundice | 4 | Hepatitis |
| 4 | Intra-abdominal neoplasm | 1 | Hemochromatosis |
| | | 1 | Infectious hepatitis |
| | | 1 | Portal cirrhosis |
| | | 1 | Biliary cirrhosis |
| 12 | Miscellaneous | 12 | (See text) |

persistent portal inflammatory reaction represented continued low grade activity of the hepatitis.

*Evaluation of Therapy in Diffuse Hepatic Disease.*—J. M., a 55 year old white woman, experienced recurrent episodes of pain and tenderness in the right upper quadrant for twenty-eight years. Cholecystectomy and appendectomy were done in 1935. On physical examination in 1947, the patient was noted to be very obese. The liver was palpable 2 fingerbreadths below the right costal margin and was smooth and nontender. Results of hepatic function tests were within normal limits. A biopsy specimen of the liver (fig. 4) revealed the presence of fatty infiltration. The patient was placed on a regimen including 16 cc. (4 Gm.) of choline [12] dihydrogen citrate N. N. R. daily. A second biopsy specimen obtained three months after the inception of therapy showed no improvement, nor did the third specimen taken three months later. The dosage of choline dihydrogen citrate was increased fourfold, and four months later (fig. 5) there was considerable diminution in the degree of fatty vacuolization.

*Recognition of Hepatic Disease.*—Table 1 reveals that liver biopsy was of particular value in correcting clinical misconceptions. This was particularly the case in acute hepatitis and portal cirrhosis, and less frequently in obstructive jaundice and intra-abdominal neoplasm. In all, biopsy resulted in a change in diagnosis in 51 of 345 cases, or approximately 15 per cent. In 12 miscellaneous cases liver biopsy caused the following changes in clinical opinion:

Biliary cirrhosis to fatty vacuolization—2
Nontropical sprue to metastatic carcinoma
Rheumatoid arthritis to acute hepatitis
Psychoneurosis to portal cirrhosis—2
Chronic passive congestion to portal cirrhosis
Hemochromatosis to portal cirrhosis
"Fatty liver" (with diabetes mellitus) to moderate portal cirrhosis
Chronic glomerulonephritis to portal cirrhosis
Sickle cell anemia to miliary granuloma
Ultimate establishment of sarcoid by lymph node biopsy

Table 2 lists the errors in biopsy diagnosis which have been made in the entire series. As is to be expected, the majority of incorrect diagnoses occurred in the presence of focal lesions which were not included in the biopsy specimen.

There were 16 biopsies reported as failures in our first paper covering 195 biopsies, resulting from lack of adequate material for examination. This figure has now been increased to 24 in a total of 403 biopsies. Although some of the failures occurred early in our experience when only a single attempt at biopsy was made regardless of the adequacy of the material obtained, the most frequent cause of failure was found to be inexperience on the part of the operator. The

TABLE 2.—*Errors in Diagnosis on Biopsy (13 Cases)*

| Case No. | Diagnosis on Biopsy | Final Diagnosis | Comment |
|---|---|---|---|
| 16 | NDAR * (2 biopsies) | Banti's disease; mild portal cirrhosis | Autopsy (last liver biopsy 6 months before death) |
| 40 | Severe bile stasis; acute cholangitis | Carcinoma of head of pancreas, with 3 small hepatic metastases | Autopsy |
| 49 | NDAR | Moderate portal cirrhosis | Autopsy |
| 77 | NDAR | Banti's disease, with "slight" cirrhosis | Splenectomy with liver biopsy |
| 83 | NDAR | Possible Chiari's syndrome; polycythemia vera | Laparotomy with liver biopsy |
| 94 | Portal cirrhosis | Portal cirrhosis with hepatoma | Autopsy |
| 98 | Severe bile stasis; acute and chronic cholangitis | Carcinoma of the head of pancreas with few small hepatic metastases | Autopsy |
| 135 | NDAR | Metastatic carcinoma of liver | Laparotomy; biopsy |
| 171 | NDAR | Carcinoma of the stomach with numerous hepatic metastases | Laparotomy with liver biopsy |
| 186 | NDAR | Metastatic carcinoma from lung; large and smooth liver, with questionable metastases | No autopsy |
| 199 | NDAR | Carcinoma of the stomach, with 3 small hepatic metastases | Autopsy |
| 220 | Bile stasis | Carcinoma of the head of pancreas, with numerous hepatic metastases | Autopsy |
| 283 | Biliary cirrhosis | Toxic cirrhosis (portal), with recent hepatic infarcts | Autopsy |

* NDAR means "no diagnostic abnormalities recognized," with the specimen presumably representing normal liver.

presence of cirrhosis accounted for some of the failures, by reason of the increased consistency of the liver and concomitant ascites. Biopsies made in apprehensive patients occasionally were unsuccessful because of lack of cooperation after the procedure was begun. The attempt was immediately discontinued if the patient

12. Syrup choline dihydrogen citrate was supplied by Flint, Eaton & Company, Decatur, Ill.

took a breath when told not to do so and no further trials were made. In a few instances, as a result of error in selecting the site of entry, it was evident that hepatic tissue was not being reached when the carrier needle was inserted to its usual depth. A second site was then chosen, treated in the usual manner, and an adequate biopsy specimen obtained without causing undue discomfort to the patient.

It is our opinion that experience with this biopsy technic is now sufficiently large to warrant wider application. Because of the danger of hemorrhage, the procedure should be carried out only by persons who have been trained in centers where this method is extensively employed. It is essential that the pathologist interpreting the biopsy material have great interest in and experience with the method in order to appreciate its advantages and limitations. We believe that the major value of needle biopsy of the liver lies in its simplicity. Although hospitalization is mandatory because of the danger to the patient, confinement need be for only a day or two.

SUMMARY

A method of performing punch biopsies of the liver using the Vim-Silverman needle is described. The indications, contraindications, reactions, failures and examples of cases demonstrating the value of the procedure are given. The safety of needle biopsy of the liver is attested by the absence of any serious reactions in 403 biopsies on 345 patients when the patients were carefully selected and carefully followed.

## ABSTRACT OF DISCUSSION

DR. FREDERICK W. HOFFBAUER, Minneapolis: Modern application of the technic of needle biopsy of the liver, stimulated by the studies of Iversen and his associates in 1939, has advanced the clinical study of hepatic disease. Needle biopsy often permits one to establish a definite diagnosis. This is particularly true in certain medical disorders in which the physical findings are not revealing and the biochemical evidences of hepatic dysfunction do not conform to any particular pattern. In the differential diagnosis of the common forms of jaundice, however, needle biopsy of the liver is necessary only in selected cases. The separation of medical from surgical cases can usually be made by clinical and biochemical studies. There are exceptions, but in the main this has been true in my experience.

DR. HANS POPPER, Chicago: The material of Dr. Schiff and his co-workers is, to my knowledge, larger than anyone else's in this country and matches what has been reported by investigators from England and Scandinavia. After sufficient histologic experience has been gained, liver biopsies may provide great help in the differential diagnosis of hepatic diseases. So far, my associates and I have encountered difficulties in histologic differentiation of early hepatic damage produced by extrahepatic biliary obstruction from toxic hepatitis. The flocculation tests did not necessarily help in this situation because, in our experience, they showed nothing abnormal in a not insignificant percentage of cases of toxic hepatitis, similar to surgical jaundice. Following jaundice of two weeks and longer, the histologic differences became clearer and the differentiation between the toxic and the surgical types of hepatitis was far easier; that was usually the time when the question of surgical intervention rendered the differential diagnosis significant. In older cases, little difficulty was encountered in the differentiation of the intrahepatic medical from the extrahepatic surgical biliary obstruction. Study of biopsy specimens of the liver has been intriguing, not only from the practical, diagnostic point of view, but also from the academic point of view of general understanding of hepatic disease. Liver biopsy may facilitate a classification of the different types of acute hepatic damage. It provides an opportunity to correlate the results of hepatic function tests with morphologic alterations and thus offers an opportunity to evaluate the function tests. Finally, it may improve the rather hazy correlation between clinical picture and pathologic changes of the liver. At present, one is often unable to decide at the autopsy table whether hepatic insufficiency was present or not. Liver biopsy may, therefore, in the future not only enable the pathologist to be of added diagnostic help to the clinician but also permit him to learn more about hepatic disease.

DR. SHEILA SHERLOCK, London, England: My colleagues and I started doing needle biopsies of the liver in 1942; since then we have performed 450 biopsies on 380 patients. Our technic was modified from that of Iversen and Roholm; we, therefore, use a trocar and cannula introduced intercostally. I do not really think there is anything to choose between this method and the use of the Vim-Silverman needle. Provided the biopsy is done after the first week or so, the distinction of obstructive from parenchymatous jaundice is usually clarified by study of the biopsy section. Supplementary evidence for the diagnosis of Hodgkin's disease, the leukemias, sarcoidosis and other such conditions can be obtained by this means. At the Postgraduate Hospital in London we do not perform a splenectomy without preliminary liver biopsy; in this way we save many persons with leukemia, myelosclerosis and hemochromatosis from unnecessary operation. As to mortality, in the first 200 biopsies we had 2 deaths. Since then we have modified our technic and taken more precautions and have had no further fatalities. Recent scrutiny of the literature shows more than 3,000 biopsies on record with 9 deaths. I do not think we ought to regard needle biopsy of the liver as an entirely safe procedure. I doubt that it ever will be, however one modifies it. It is a method one must use in well appointed institutions on carefully selected patients with personal supervision by the physician for twenty-four hours after the puncture and with facilities available for transfusion if necessary. With these provisos, it is a reasonably safe and justifiable procedure.

DR. IRVING B. BRICK, Washington, D. C.: For the past eighteen months my associates and I have done these needle biopsies without sequelae; however, I have noticed gross bleeding through the needle in some cases. Four of every 5 we performed were successful biopsies. I should like to know your average.

DR. LEON SCHIFF, Cincinnati: The Section has been fortunate in having Dr. Hoffbauer, Dr. Popper and Dr. Sherlock discuss our presentation. They are all outstanding in this field and their contributions have been a stimulus in our own studies. In answer to Dr. Brick's question, when we first started doing liver biopsies, our failures were approximately 40 per cent. Our failures now are 5 or 6 per cent, and Dr. Sherlock tells me that her experience coincides with ours. Another means of decreasing the percentage of failures is taking more than one piece of tissue at the time of biopsy. If one fails to obtain a specimen on the first attempt, a second or third attempt should be made at the time of the original biopsy. I might add that, contrary to theoretic expectations, we have noted no increase in frequency of reaction following repeated attempts at biopsy, but that probably is a matter of luck. Is there a "safest" procedure from a technical point of view? Is there a safest approach? I presume the answers to these questions will be forthcoming. One note of caution regarding the anterior approach: I have seen 2 patients who presented what was thought to be a large liver due to the presence of neoplasm. Through blissful ignorance a biopsy specimen was obtained through the transpleural approach, only to find at operation that we were dealing with a tumor of the proximal portion of the transverse colon adherent to the liver instead of neoplasm of the liver! Had we taken the biopsy specimen through the anterior approach, we might have perforated the colon. In regard to the question of bleeding at the site of the incision of the skin, we have done only a few biopsies with the Iversen-Roholm technic; with the Vim-Silverman needle we have noted it on rare occasions.

# AUREOMYCIN IN PRIMARY ATYPICAL PNEUMONIA

## A Controlled Evaluation

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Several reports have already appeared presenting evidence that aureomycin is an effective therapeutic agent in primary atypical pneumonia.[1] All have described the course of the disease in relatively small groups of patients treated with aureomycin. None have presented data on comparable numbers of patients ill during the same period of time who did not receive aureomycin. While the remarkable uniformity of the therapeutic response constitutes a strong argument for the effectiveness of the drug, a certain amount of doubt persists because the course of the disease is exceedingly variable.

Primary atypical pneumonia is exceptionally well suited for controlled evaluation of therapeutic agents. In certain population groups cases may occur in large numbers. The febrile course is long enough in a proportion of the patients to permit the demonstration of a definite shortening of the disease. The fatality rate in young persons is extremely low, making it justifiable to withhold specific therapy from a portion of the patients. No previously available therapeutic agent had been found effective. In view of these considerations, when a suitable opportunity arose, it seemed highly desirable to conduct a study of parallel groups of patients, one of which received aureomycin while the other did not. The present report presents the results of such a study carried out at Fort Ord, California, during the winter of 1948-1949.

### MATERIAL AND METHODS

*Selection of Patients.*—Starting Dec. 5, 1948, all patients with acute respiratory disease admitted to wards at the Station Hospital, Fort Ord, who met all of the following criteria were included in the study group: (*a*) The clinical course and physical observations suggested that the patient had primary atypical pneumonia rather than bacterial pneumonia[2]; (*b*) the roentgenogram of the chest showed unequivocal evidence of pneumonia; (*c*) the patient's temperature was 102 F., or higher, during the twenty-four hours prior to institution of treatment; (*d*) the white blood cell count was less than 12,750, and (*e*) the patient did not appear to be showing significant improvement. Adherence to these criteria necessitated exclusion of slightly more than half the patients admitted to the hospital during the study period whose course suggested that they had primary atypical pneumonia.

*General Plan for Selection of Therapy.*—Patients meeting all the criteria outlined were included in the study group. Alternation was accomplished with 30 patients, half of whom received aureomycin and half penicillin. Elimination of certain patients because they failed to meet certain criteria (e. g., roentgen observations were considered equivocal) on occasion disturbed the strict alternation, but the selection remained, as nearly as possible, a random one. In this group of 30, 15 patients on a fixed aureomycin schedule were compared with a similar group on a fixed penicillin schedule.

During the same period 5 additional patients received penicillin shortly after admission to the wards and were subsequently found to meet all criteria for inclusion in the study group. These were balanced in part with 3 similar patients who were given aureomycin, in 2 instances by the intravenous route. Since the inclusion of these patients did not appear to alter the similarity of the groups treated with the two drugs (table 1), results obtained with these 8 patients are presented together with those obtained in the 30 previously described.

TABLE 1.—*Comparison of Aureomycin-Treated and Penicillin-Treated Groups Prior to Therapy*

| | Number of Patients | |
|---|---|---|
| | Aureomycin | Penicillin |
| **Age** | | |
| 17-20 | 12 | 14 |
| 21-30 | 6 | 6 |
| **Duration of fever, days** | | |
| 1-4 | 7 | 8 |
| 5-7 | 9 | 10 |
| 8-11 | 2 | 2 |
| **Maximum temperature (F.)** | | |
| 102-104 | 10 | 12 |
| 104-106 | 8 | 8 |
| **Admission white blood cell count** | | |
| 5,000-10,000 | 16 | 14 |
| 10,000-13,000 | 2 | 6 |
| **Positive observations in roentgenogram of chest** | 18 | 20 |
| **Total number of patients** | 18 | 20 |

A final group of 4 patients consisted of persons who at the start received penicillin and then were given aureomycin. This was done when, after at least forty-eight hours' treatment with penicillin, the patient's condition had obviously become worse and was moderately alarming.

Penicillin was selected for use in the control group for two reasons. First, it was considered desirable to administer some preparation and, prior to the study, penicillin had been generally used in the hope of shortening the course of the disease. Second, it was reasoned that, if patients with bacterial pneumonia were inadvertently included in the series, any therapeutic response obtained with aureomycin would tend to be

This study was carried out under the auspices of the Commission on Influenza, Army Epidemiological Board.

The aureomycin used in this study was supplied by the Lederle Laboratories, American Cyanamid Corporation.

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From the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley; the Division of Medicine, University of California Medical School, San Francisco; and the Medical Service, Station Hospital, Fort Ord, California.

We received assistance from Dr. E. H. Lennette, Chief, Viral and Rickettsial Disease Laboratory, and Associate Member of the Commission on Influenza; Dr. T. Francis Jr., Chairman, Commission on Influenza; Col. A. L. Gorby, 6th Army Surgeon, Presidio, San Francisco; Col. J. L. Murchison, Major W. G. Thalmann Jr., Capt. E. Stratton, Capt. A. J. Castagno, Miss Claudine Conway, R.N., Mrs. Phyllis Sands, and other personnel at Fort Ord; and from Col. F. E. Council and Capt. D. L. Weiss at the 6th Army Medical Laboratory, Fort Baker.

1. Schoenbach, E. B., and Bryer, M. S.: Treatment of Primary Atypical Non-Bacterial Pneumonia with Aureomycin, J. A. M. A. **139**: 275-280 (Jan. 29) 1949. Kneeland, Y., Jr.; Rose, H. M., and Gibson, C. D.: Aureomycin in Treatment of Primary Atypical Pneumonia, Am. J. Med. **6**: 41-50 (Jan.) 1949. Finland, M.; Collins, H. S., and Wells, E. B.: Aureomycin in the Treatment of Primary Atypical Pneumonia, New England J. Med. **240**: 241-247 (Feb. 17) 1949.

2. Meiklejohn, G.: Viral Pneumonia, M. Clin. North America **31**: 1442-1456 (Nov.) 1947.

canceled out if penicillin were used in the alternate group. This would not be the case if no therapeutic agent were used in the control group. It was our opinion, on the basis of previous experience with penicillin, that the drug was not an effective therapeutic agent in the treatment of primary atypical pneumonia.

*Dosage.*—Aureomycin therapy was instituted with an intravenous injection of 50 mg. of aureomycin hydrochloride in 5.0 milliliters of a leucine diluent, which contained 131 mg. of L-leucine in 5.0 milliliters, and an oral dose of 1.0 Gm. Thereafter, patients received 1.0 Gm. of drug by mouth every six hours until their temperatures had been normal for at least forty-eight hours. In a number of instances treatment was continued for a longer period. In a small number of cases, when the orally administered drug was poorly tolerated, one or more intravenous injections of 50 mg. of aureomycin were given along with the customary oral doses. At the conclusion of the study a small number of patients were treated on a regimen of 100 mg. intravenously each six hours during the day and a single oral dose of 1.0 Gm. during the night. Penicillin was administered by the intramuscular route in doses of 100,000 units of aqueous penicillin every six hours.

TABLE 2.—*Comparison of Duration of Fever After Commencement of Treatment with Aureomycin and Penicillin*

| | Febrile * Course (Days) | | | | | | |
|---|---|---|---|---|---|---|---|
| Therapy | <1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-10 | 10 or More |
| | Number of Patients | | | | | | |
| Aureomycin | 8 | 5 | 2 | 2 | 1 | 0 | 0 |
| Penicillin | 3 | 3 | 2 | 3 | 2 | 3 | 4 |

*Defined as day with oral temperature in excess of 99 F.

*Laboratory Procedures.*—Complete blood cell counts, urinalysis and roentgenograms of the chest were routine procedures. These were repeated for the most part at weekly intervals. In most patients stained sputum smears were examined, and sputum and blood cultures were taken prior to treatment. The latter were uniformly sterile. It is worthy of comment that bacterial pneumonias were uncommon during this period.

Blood specimens were collected after admission and at weekly intervals thereafter for at least two weeks. Cold agglutination tests were done immediately at the Station Hospital Laboratory. Serums were then shipped to the 6th Army Laboratory at Fort Baker, where agglutination inhibition tests for influenza A and B were performed. Subsequently, complement fixation tests for influenza A and B, psittacosis and Q fever were run at the Viral and Rickettsial Disease Laboratory in Berkeley.

*Aureomycin Serum Levels.*—Two sets of serum were collected for the determination of aureomycin levels from 7 of the patients treated with aureomycin. The first set was collected one, two, four and six hours after the institution of therapy and the second set forty-eight hours later, when specimens were taken two, four and six hours after an oral dose of 1.0 Gm. Serum was removed from the clot as soon as possible and immediately placed in a carbon dioxide ice chest. Specimens were stored at temperatures below — 45 C. until tested by methods described elsewhere.[3]

*Clinical Study.*—All patients were examined by, and followed by, one of us (R. I. S.) as well as by the medical ward officers. Complete records were kept of clinical response and of any evidence of aureomycin toxicity.

Dating the onset of illness caused considerable difficulty, because many persons gave a history of respiratory symptoms, especially cough, from the time of arrival on the post. The date of onset (first day of disease) was interpreted as the day on which symptoms of feverishness or chilliness and exacerbation of previous symptoms were noted.

Patients are identified in the text with one of three prefixes followed by a serial number. Thus, A-1 indicates patient 1 in the aureomycin-treated series; P-1, the same in the penicillin-treated group; and P-A 1, the first in the group started on penicillin and shifted to aureomycin.

*Comparability of Aureomycin-Treated and Penicillin-Treated Groups.*—Since the validity of any conclusion reached as a result of a controlled study such as this rests on the premise that the two groups are truly comparable, at the conclusion of the study an analysis was made of various factors present at the time of institution of treatment. No significant differences were found with respect to the duration of the disease when treatment with the drug was started, or the maximum temperatures prior to therapy. In the aureomycin-treated group a slightly larger proportion of persons fell in the age group over 20 years, while in the penicillin-treated group a somewhat larger proportion of persons had admission white blood cell counts in excess of 10,000. Roentgen observations defied quantitative analysis, but appeared to be in general similar. A summary of these data is presented in table 1. It was concluded that the two groups were remarkably alike in composition.

## RESULTS

*Penicillin-Treated Group.*—Decided variation in the time required for symptomatic improvement and defervescence was observed in this group of patients. Six of the 20 became afebrile within forty-eight hours after penicillin therapy was started. The febrile courses of the remainder continued for longer periods. In 2 patients fever persisted for as long as twenty-two and twenty-three days, respectively. A summary of the duration of the febrile course is presented in table 2. Symptomatic improvement and clearing of physical and roentgen observations tended to lag behind the drop in temperature. In many instances cough, anorexia and weakness of pronounced degree persisted after the patient became afebrile.

Several patients obviously became worse while receiving penicillin, with rise in temperature, extension of pneumonia and appearance of, or increase in, dyspnea and cyanosis. In 4 of these patients there developed a picture sufficiently alarming to cause discontinuance of penicillin and administration of aureomycin. These patients are discussed in a subsequent section. More frequently, while the patient received penicillin, little

3. Brainerd, H. D.; Bruyn, H. B.; Meiklejohn, G., and Scaparone, M.: Assay of Aureomycin in Body Fluids: Observation on Individuals Receiving Aureomycin, Proc. Soc. Exper. Biol. & Med. **70**: 318-321 (Feb.) 1949.

immediate change was noted in the course of the disease, which dragged on at a somewhat lower level of severity for a considerable number of days.

In summary, while approximately one third of the patients treated with penicillin recovered within forty-eight hours, the courses in the remaining two thirds argue strongly against the drug's being an effective therapeutic agent. In a disease as variable as primary atypical pneumonia a similar distribution has been observed in untreated patients[4] and might well be observed in any group of patients treated with drugs lacking specific effects. It may be noted that the over-all picture in the penicillin-treated group would probably appear even more unfavorable if the 4 most seriously ill patients had not been removed from this group and given aureomycin.

*Aureomycin-Treated Group.*—In contrast to the penicillin-treated group, all patients treated with aureomycin showed definite symptomatic improvement within three days; in most instances sooner. Twelve of the 18 patients became afebrile within forty-eight hours after therapy was started, and an additional 3 patients within seventy-two hours. Two of the remaining 3 became afebrile within ninety-six hours, and the third was afebrile within one hundred and twenty hours. In other words, 15 of the 18 persons were afebrile within three days after treatment with the drug was begun, and in no instance did fever persist during administration of drug for as long as five days (table 2).

Aureomycin therapy was discontinued in 4 patients between forty-eight and seventy-two hours after the temperature became normal, in 6 between seventy-two and ninety-six hours, in 5 between ninety-six and one hundred and twenty hours and in 2 more than one hundred and twenty hours after defervescence. All patients appeared to be well on the road to recovery when treatment with the drug was stopped, and in 15 of the 18 convalescence continued in an uneventful way. It was the impression of the attending physicians that the clearing of the physical signs and roentgen observations was somewhat more rapid than expected, though these lagged behind the symptomatic improvement of the patient.

The remaining 3 persons (A-11, A-12 and A-15) showed definite evidence of clinical relapse from three to six days after aureomycin therapy was discontinued. Each of the 3 began to have a low grade fever. More important, roentgenograms of the chest, which had in each instance begun to show evidence of clearing, showed evidence of recurrence or extension of the pneumonic area. This suggested a flare-up of the original disease rather than the acquisition of a new disease while the patient was in the ward for disease of the respiratory tract. Two of the patients, because they had white blood cell counts of 15,200 and 29,100, respectively, were given penicillin. Fever persisted until aureomycin was substituted for penicillin. Both these patients and the third, who had not received penicillin, became afebrile within twenty-four hours after aureomycin therapy was reinstituted. Recovery was uneventful thereafter. A summary of the history of case A-12 is presented as an example of this sequence.

CASE 1 (Fig 1).—Patient A-12, a 17 year old boy, was admitted to the hospital with a hacking cough of ten days' duration. Three days prior to entry the cough had become severer and occasionally productive of bloody sputum and was accompanied with pain under the upper part of the sternum. He had also noted dyspnea on exertion, feverishness, chilly sensations, occasional transitory aches in the legs, slight sore throat, nausea, decided malaise, weakness and watery diarrhea.

On admission, physical examination revealed a slight degree of cyanosis of the lips and nail beds, scattered sibilant rhonchi with dulness and crepitant rales at the left base, and a slightly enlarged left anterior cervical lymph node. The white blood cell count was 6,600. Urinalysis showed a trace of albumin and 4 to 6 white blood cells and 1 granular cast per high power field. Sputum smear and culture showed occasional gram-positive diplococci. No growth was observed in a blood culture.

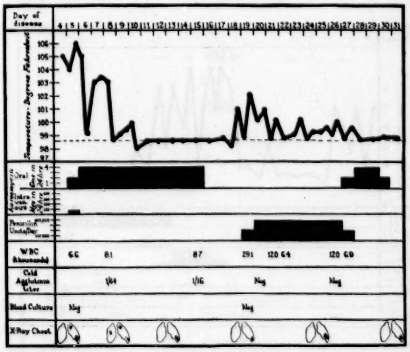


Fig. 1 (case A-12).—Illustration of relapse at discontinuation of aureomycin therapy.

On the second hospital day, after the temperature had reached 105.8 F. (oral), the patient was given aureomycin, 50 mg. intravenously and 1.0 Gm. orally, followed by 1.0 Gm. orally every six hours. Although the patient vomited about two hours after the first dose, he was able to retain succeeding doses and showed a precipitous drop in temperature within twenty-four hours. However, there ensued persistent vomiting of his medication, so that he was unable to retain any for about twenty-four hours. This was associated with another rise in temperature to a maximum of 103.6 F. (orally) on the morning of the eighth day of illness. Thereafter the temperature fell gradually to normal on the tenth day of disease. Aureomycin determinations on the fifth and seventh days of disease showed serum levels of 5.0 micrograms per milliliter.

Convalescence thereafter progressed satisfactorily, and the aureomycin therapy was discontinued on the twelfth hospital day, after the patient had been afebrile for six days. The patient still complained of weakness with exertion and a slight degree of anorexia, but otherwise had no untoward complaints. Pulmonary observations were minimal and consisted of crackling rales at both bases. Roentgenograms, which had revealed a pneumonic process in the left base on admission, had shown steady and progressive clearing, so that by the fifteenth hospital day only a minimal amount of ragged increased density in the left cardiophrenic angle was observed.

4. (*a*) Dingle, J. H.; Abernethy, T. J.; Badger, G. F.; Buddingh, G. J.; Feller, A. E.; Langmuir, A. D.; Ruegsegger, J. M., and Wood, W. B., Jr.: Primary Atypical Pneumonia, Etiology Unknown, Am. J. Hyg. **39**: 67-128 (Jan.) 1944; 197-268 (March); 269-336 (May) 1944. (*b*) Young, L. E.; Storey, M., and Redmond, A. J.: Clinical and Epidemiological Features of Primary Atypical Pneumonia of Unknown Etiology Among Hospital and Medical School Personnel, Am. J. M. Sc. **206**: 756-769 (Dec.) 1943. (*c*) Finland, M.; Peterson, O. L.; Allen, H. E.; Samper, B. E., and Barnes, M. W.: Cold Agglutinins: II. Cold Isohemagglutinins in Primary Atypical Pneumonia of Unknown Etiology with a Note on the Occurrence of Hemolytic Anemia in These Cases, J. Clin. Investigation **24**: 458-473 (July) 1945.

Seventy-nine hours after the aureomycin therapy had been discontinued and associated with the patient's first ambulation, there was a recurrence of fever (temperature was 100.6 F., orally) along with increased cough productive of mucopurulent sputum, constricting sensation across lower right side of the chest, malaise, chilliness and slight sore throat.

The white blood cell count on the second day of this febrile episode was 29,100 per cubic millimeter, with 90 per cent polymorphonuclear cells. Smear of the sputum revealed mixed flora with a predominance of organisms resembling streptococci. Culture of the sputum yielded only gram-negative diplococci, and blood culture was subsequently reported as being sterile.

Because of the leukocytosis and high proportion of polymorphonuclear cells in the differential count, it was thought that the patient might be suffering from a bacterial complication. Penicillin, 100,000 units of the aqueous solution, was given every six hours. However, the patient continued to have a low grade fever, associated with aggravation of symptoms and physical signs as well as roentgen evidence of a reinvolvement of the previously clearing left base.

After seven days of penicillin therapy, aureomycin therapy in the dosage previously outlined was reinstituted, with return of the temperature to normal levels in twelve hours. Aureomycin therapy was again discontinued after sixty-eight hours.

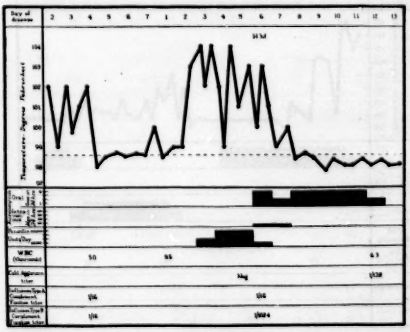

Fig. 2. (case P-A 2).—Illustration of initial attack of influenza B followed by primary atypical pneumonia, failure of the patient to improve with penicillin therapy and the prompt response to aureomycin.

Although the physical signs of pulmonary parenchymal involvement were slow in clearing, the patient claimed definite subjective improvement soon after the reinstitution of aureomycin therapy. The cold agglutinin titer was 1:64 on the eighth day of illness and fell off thereafter.

*Comment.*—This patient's course illustrates exceptionally severe primary atypical pneumonia in which the response to aureomycin, though slow, was satisfactory. Treatment during the first three days was difficult because of repeated vomiting. Despite the fact that aureomycin was continued for five days after the temperature returned to normal, recurrence of fever and evidence of reactivation of the pneumonia occurred within three days after treatment with the drug was stopped. This was accompanied with a leukocyte count of 29,100 with a differential count of 90 per cent polymorphonuclear cells. Fever persisted for seven days while penicillin was given and disappeared within twenty-four hours when aureomycin was given for the second time.

*Patients Treated First with Penicillin and Then Aureomycin.*—Four patients fell in this group. All had failed to show evidence of improvement after forty-eight to ninety-six hours of treatment with penicillin and were then given aureomycin because they appeared seriously ill. In each instance decided symptomatic improvement and drop in temperature to normal followed within forty-eight hours after the institution of aureomycin treatment. A résumé of the course of patient P-A 2 is presented as an example of this type of case.

Case 2 (Fig. 2).—Patient P-A 2, an 18 year old male patient, was admitted with a history of having had a mild nonproductive cough for three weeks. On the day prior to admission he noted increased cough, feverishness, chilly sensations, generalized myalgia, sore throat and intermittent headache and coryza. Results of the physical examination on admission were essentially negative apart from fever (102 F., oral), slight congestion of the palpebral conjunctivas and moderate congestion of the pharynx. The white blood cell count was 5,000.

The patient was treated with symptomatic drugs. On the fourth day of the disease he became afebrile. Complaints of slight coryza, sore throat and cough persisted. Serum specimens collected on the fifth and thirteenth days of disease were tested against influenza A and B viruses, and a diagnosis of influenza B was established by both complement fixation and agglutination inhibition tests.

Five days later the patient's temperature rose sharply to 103 F. There were no complaints, other than the sensation of being feverish, or abnormal physical observations. The white blood cell count had been 9,500 on the previous day. Sputum studies failed to disclose any preponderant organism. The following day the patient suffered from decided malaise, generalized aches and pains, anorexia and recurrence of nonproductive cough. The pharynx was injected, and dulness to percussion was noted over both bases, with occasional crackling rales at the right base. A roentgenogram of the chest on Jan. 13, 1949, revealed a homogeneous density overlying the lateral half of the right hemidiaphragm.

Treatment with aqueous penicillin, in doses of 100,000 units intramuscularly every six hours, was begun. During sixty-six hours on this regimen the patient's condition appeared to become worse, with continued temperature elevations to 103 and 104 F. A second roentgenogram, on January 15, showed infiltrations at both bases. Penicillin therapy was then discontinued and aureomycin therapy started, with 50 mg. given intravenously and 1.0 Gm. orally at the start followed by 1.0 Gm. every six hours. Because of persistent headache and slight meningismus, lumbar puncture was done. Spinal fluid observations were within normal limits. Rapid subjective improvement was noted, and the patient was afebrile within thirty-six hours after aureomycin therapy was started. Convalescence was uneventful.

*Comment.*—It is of interest that a patient admitted with influenza B became ill with primary atypical pneumonia before discharge from the hospital. The case illustrates well the lack of effect of penicillin in the latter disease and the dramatic response which is often noted with aureomycin therapy.

*Comparison of the Course of Aureomycin-Treated and Penicillin-Treated Patients.*—Differences between the two groups are brought out most readily by comparison of the duration of the febrile course of one group with that of the other after treatment was begun. For this analysis any oral temperature reading in excess of 99 F. was considered to indicate an active infectious process, since even low grade fever was occasionally associated with recrudescence or a protracted convalescence. When data from the two groups are presented in tabular form (table 2), the difference is striking. The bulk of the aureomycin-treated patients fell in the groups which became afebrile within three

days. In contrast, the majority of the penicillin-treated patients continued to be febrile for three days or more, and 7 of the 20 remained febrile for more than five days. Arithmetic means were not calculated because the excessive duration of the course in a few patients was considered to invalidate any figure obtained in groups as small as these.

TABLE 3.—*Maximum Cold Hemagglutinin Titers in Aureomycin-Treated and Penicillin-Treated Groups*

| Therapy | No. of Patients | Number of Patients with Titers of | | | | |
|---|---|---|---|---|---|---|
| | | 8 or Less | 16 | 32 | 64 | 128 or More |
| Aureomycin | 18 | 6 | 6 | 3 | 2 | 1 |
| Penicillin | 20 | 6 | 2 | 1 | 6 | 5 |

Because the type of presentation used herein fails to take into account any difference between a temperature of 99 or 106 F., a more complete record was prepared in the form of miniature temperature charts of each patient before and after treatment (fig. 3). This method has the advantages of showing the course of the disease more accurately and of making clear the time relationship of the response, or lack of response, to the administration of drug. Again the relative uniformity of response with aureomycin is brought out, while the varied response to penicillin is apparent.

*Cold Hemagglutination Tests.*—In the penicillin-treated group, cold agglutinins were demonstrated in significant titer (32 or more) in serums from 12 of the 20 subjects. In the patients with a more protracted course, a greater proportion of persons had cold agglutinins in significant titer. Thus, only 3 of 9 patients with febrile courses of less than seven days had titers of 32 or more, while 9 of 11 patients with a course longer than eight days had similar titers. This is in line with earlier observations.[5]

TABLE 4.—*Aureomycin Serum Levels in 7 Patients*

| Patient | Aureomycin Serum Level * Following Initial Dose † After | | | | Aureomycin Serum Level * 48 Hours Later ‡ | | |
|---|---|---|---|---|---|---|---|
| | 1 Hr. | 2 Hr. | 4 Hr. | 6 Hr. | 2 Hr. | 4 Hr. | 6 Hr. |
| A-7 | 5.0 | ... | ... | 5.0 | 5.0 | 2.5 | 2.5 |
| A-9 | ... | 5.0 | 10.0 | 5.0 | 5.0 | ... | 1.25 |
| A-11 | 1.25 | 5.0 | 2.5 | 1.25 | 10.0 | 2.5 | 1.25 |
| A-12 | 2.5 | 2.5 | 5.0 | 5.0 | 5.0 | 5.0 | 5.0 |
| A-14 | 0.3 | 0.15 | 0.6 | 1.5 | 10.0 | 1.25 | 1.25 |
| A-15 | ... | 2.5 | 0.6 | 0.6 | 5.0 | 2.5 | 2.5 |
| A-88 | ... | 1.25 | 0.6 | ... | 1.25 | 1.25 | 0.6 |

* Micrograms per milliliter.
† The initial dose was 50 mg. given intravenously and 1 Gm. orally.
‡ After 1.0 Gm. given orally.
§ This patient was treated with 100 mg. intravenously for six hours during the day with a single night dose of 1.0 Gm. The drug was not given orally during twelve hours preceding the second series.

The results in the aureomycin-treated patients were somewhat different. Only 6 of the 18 were found to have titers of 32 or more. In the persons with an illness of less than seven days the picture was similar to that of the other group in that 4 of 11 had elevated titers. However, in the patients with a longer course, only 2 of 7 had titers above 32. There was a further difference between the groups treated with the two drugs in that considerably fewer titers as high as 64 and 128 or more were encountered in the aureomycin-treated group (table 3).

*Serologic Tests for Influenza, Psittacosis and Q Fever.*—With the exception of 1 patient, P-A 2, significant rises in antibody to these agents were not observed in any subjects.

*Leukocyte Response.*—In the whole study group (42 patients) there were 6 who showed elevation of total white cell count. These ranged from 17,000 to 29,100, with differential counts showing that the bulk of the increase was due to the polymorphonuclear cells.

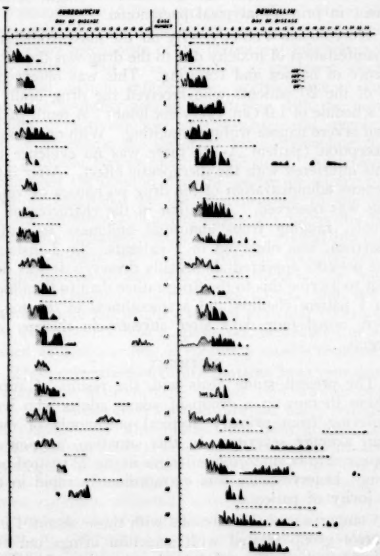

Fig. 3.—Comparison of temperature charts of aureomycin-treated group and penicillin-treated group. The shaded area represents the temperature record before treatment, and the black areas after treatment. The arrows indicate the period during which the drug was given.

It will be recalled that white cell counts at the time of admission had in all instances been below 12,750. The leukocytosis occurred during the third and fourth weeks after onset. There was nothing to suggest secondary bacterial infection as a cause of this response. Two of the patients were treated with penicillin during this phase without effect, and then responded promptly to aureomycin. This late leukocytosis has been noted before [6] and is of practical importance, since it should be realized that, in a patient with pneumonia seen two weeks or more after onset, a high white cell count does not necessarily favor the diagnosis of a bacterial as against a viral pneumonia.

5. Finland, Peterson, Allen, Samper and Barnes.[4c] Meiklejohn, G., and Hanford, V. L.: Agglutination Tests with Streptococcus No. 344 in Primary Atypical Pneumonia, Proc. Soc. Exper. Biol. & Med. **57**: 356-358 (Dec.) 1944.

6. Young, Storey and Redmond.[4b] Meiklejohn, G.; Eaton, M. D., and van Herick, W.: A Clinical Report on Cases of Primary Atypical Pneumonia Caused by a New Virus, J. Clin. Investigation **24**: 241-250 (March) 1945.

*Aureomycin Serum Levels.*—A summary of the serum levels obtained with two sets of specimens from each of 7 patients is presented in table 4. It will be noted that measurable levels were in all instances present within two hours after treatment was started. The initial 50 mg. intravenous dose, coupled with the oral dose of 1.0 Gm., thus appeared to avoid any appreciable lag in achievement of readable serum levels. While most levels fell between 1.25 and 10.0 micrograms per milliliter, there was considerable individual variation. No data are available which permit any statement regarding levels desirable for therapeutic response. Since a good response was observed in all these patients, and, since others have reported favorable therapeutic responses on smaller dose schedule, it is reasonable to assume that a lower level might be sufficient in primary atypical pneumonia.

*Aureomycin Toxicity.*—By far the most troublesome manifestation of toxicity due to the drug was the occurrence of nausea and vomiting. This was observed in 9 of the 20 patients who received the drug orally on a schedule of 1.0 Gm. every six hours. A tenth patient had severe nausea without vomiting. With one possible exception (patient A-12) there was no evidence that this interfered with the therapeutic effect. After intravenous administration of the drug no nausea or vomiting was observed. Alteration in the character of the stools, ranging from abnormal bulkiness to watery diarrhea, was observed in 5 patients. In 2 instances the patients appeared abnormally drowsy. It was difficult to ascribe this to the drug rather than to the illness. In 1 patient cheilitis and a smoothness of the tongue were noted four days after aureomycin therapy was begun.

## COMMENT

The present study deals with the results of aureomycin therapy in a group of young adults who were suffering from primary atypical pneumonia of more than average severity. In this situation, aureomycin appeared to be uniformly effective in the 22 treated persons. Defervescence was extraordinarily rapid in the majority of patients.

Comparison of these results with those obtained in a control group treated with penicillin brings out two points: first, that a substantial proportion of patients treated with the latter drug recovered soon after institution of therapy; second, that proof of aureomycin effectiveness rests largely on the fact that the protracted type of course observed in a number of the penicillin-treated patients was eliminated. Stated in another way, with patients of the type included in this study, prompt recovery occurred in almost half of the control group. Results with aureomycin could thus be compared only with results in the other half. The actual test of the drug lay in our determining whether, instead of obtaining prompt recovery in only half of the patients, it would be possible to obtain prompt recovery in all. This test appears to have been met.

One point which should be stressed is that relapse apparently may occur in aureomycin-treated patients even when treatment with the drug is continued for several days after the temperature has returned to normal. There was no evidence of reactivation of the disease while patients were receiving the drug, but 3 of the treated patients appeared to relapse after treatment with the drug was stopped. This is not surprising in view of previous experience with aureomycin in Q fever.[7] It is reassuring that aureomycin appeared to be as effective in treating the relapse as the initial episode.

The reappearance of cases of primary atypical pneumonia at a military induction center is of some interest. The relatively high incidence of the disease is brought out by the fact that almost one fifth of the patients admitted to the wards for diseases of the respiratory tract during the period of the study were ill with primary atypical pneumonia. The clinical picture was in virtually all respects similar to that observed during epidemics in the early years of World War II.

Cold agglutinins in significant titer were found in substantially the same proportion of patients who were treated with penicillin as in previously studied groups of comparable severity. Agglutinin titers were less frequently above the normal range and tended to be lower in the subjects treated with aureomycin. Since the two groups were similar prior to therapy, it seems not unlikely that treatment with aureomycin suppressed the formation of the cold hemagglutinins. If this proves to be true, the usefulness of the cold agglutination test as a means of confirming the diagnosis of primary atypical pneumonia may be reduced.

A few words might be added in conclusion about the necessary dose of drug and about toxicity. It seems likely that smaller doses may prove adequate. With the oral dosage used in this study, 4.0 Gm. per day, nausea and vomiting occurred with distressing frequency. Both smaller oral dosage and parenteral administration of the drug may offer more satisfactory therapeutic regimens.

## SUMMARY

Prompt therapeutic response was observed in 22 patients with primary atypical pneumonia treated with aureomycin. Definite variation in the duration of the disease was observed in a control group of 20 patients treated with penicillin. Comparison of the duration of fever in the two groups indicates that penicillin is not an effective drug and that aureomycin is highly effective in primary atypical pneumonia. Apparent clinical relapse was observed in 3 patients after aureomycin therapy was stopped. Each responded rapidly when treatment with the drug was resumed. Cold agglutinins in significant titer were demonstrated in 12 of 20 patients in the control group and in a smaller proportion of the aureomycin-treated group.

7. Lennette, E. H.; Meiklejohn, G., and Thelen, H. M.: Treatment of Q Fever in Man with Aureomycin, Ann. New York Acad. Sc. **51**: 331-342 (Nov. 30) 1948.

**Excessive Deaths in Chicago from Air Pollution.**—Based on the low rates prevailing in its clean suburbs, Chicago each year has an excess of 258 deaths from pneumonia among white males in its dirtier districts, 241 from tuberculosis and 69 from buccal and respiratory tract cancers—a total of 568 deaths among white males each year from these three respiratory diseases alone in excess of the death rates these diseases show in the city's cleanest districts. Add to this one-tenth as many deaths for white females and for Negro males, and a grand total is obtained of roughly 700 deaths each year, which represents a measure of the respiratory hazard of living in Chicago's dirtier districts.—Clarence A. Mills and Marjorie Mills-Porter, M.D., *Occupational Medicine*, June 1948, page 633.

# D-TUBOCURARINE IN OIL-WAX SUSPENSION IN RHEUMATOID SPONDYLITIS

## Its Use as an Adjuvant

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Rheumatoid spondylitis is a chronic progressive disease of unknown causation, involving the sacroiliac joints, the posterior intervertebral (apophyseal) joints, the costovertebral and costochondral junctions and the longitudinal spinal ligaments. This disease is characterized by pain and limited motion of the spine, spasm of the paravertebral muscles, frequent flexion deformity of the spine, limited chest expansion and systemic manifestations of fatigue, loss of weight and strength. Fortunately, proper treatment will relieve the majority of the patients. This treatment consists of roentgen therapy to the spine (which will benefit 90 per cent [plus or minus]), systemic therapy, physical therapy and measures to correct and maintain proper posture (such as spinal brace, postural exercises, bed rest and bed boards). This regimen will relieve pain and prevent deformity in most patients, so that if ankylosis occurs, the spine will be in a position of extension and the chest in full expansion.

The few persons who are not relieved of pain and muscle spasm, and in whom flexion deformity develops, require prolonged, expensive and uncomfortable hospital treatment. Absolute bed rest, firm mattress with bed boards or a Bradford frame and orthopedic measures, such as body casts or skeletal traction, are needed to correct the deformity and produce extension of the spine. One of the most impressive manifestations of the disease in the latter group of patients is the obvious spasm of the paravertebral muscles (extensors of the spine). Since motion is limited in all directions and flexion deformity is frequent, the flexor muscles of the spine are necessarily involved in a similar state of contraction. Consequently, successful treatment of the muscle spasm will be of great benefit to the patient.

Muscle spasm is a state of involuntary muscle contraction which is characterized by pain and resistance to attempted stretching. In rheumatoid spondylitis, it is a reflex protective mechanism to produce splinting and prevent motion of the involved vertebral structures. While it is true that muscle spasm is caused by the pain, we feel that much of the pain (and also the limited motion) is in turn produced by the muscle spasm, thus establishing a vicious cycle of pain. Not only does this cycle become self perpetuating, but the threshold of the neural arc is lowered and the response becomes abnormally active (stimuli outside the normal range of frequency will elicit muscle response). In an attempt to interrupt this vicious cycle, we have resorted to many measures, among them, intensive physical therapy, procaine hydrochloride injections, neostigmine (prostigmin®) injections and injections of the aqueous solution of curare. Unfortunately, none of these methods have been very efficacious or practical in rheumatoid spondylitis. It is true that the aqueous solution of curare did produce muscular relaxation, but it was necessary to inject an amount sufficient to produce the unpleasant side effects of curarization (diplopia, generalized muscular weakness, inability to lift the head, difficulty in swallowing and even breathing). Muscular relaxation was transient and persisted only for three to four hours, and maintenance of this level was impractical. However, the preparation of an oil-wax suspension of d-tubocurarine chloride by Schlesinger,[1] which produced prolonged muscular relaxation devoid of the usual side effects of curarization in a group of patients with "acute low back syndromes,"[2] suggested its use in patients with rheumatoid spondylitis.

The mechanism of muscular relaxation by curare requires some explanation of its action on the myoneural junction. Tubocurarine (the pure crystalline compound isolated from curare) has the ability to block neuromuscular transmission at the junctional region. The exact mechanism of the myoneural junction is still unexplained, but it is probably a combined electrochemical action induced by acetylcholine. Tubocurarine probably acts by interfering with the normal action of acetylcholine on the myoneural membrane or by increasing the threshold for acetylcholine above the available concentration of the drug. Schlesinger[3] expressed the opinion that the degree of curare block can be controlled by the concentration of the drug at the myoneural junction. This fact forms the basis of curare therapy—that a partial or critical block can be established which will prevent transmission of abnormal stimuli and thus reduce the abnormal muscle activity (spasm) while normal stimuli will not be blocked and will produce normal muscular contraction. In this manner, muscle spasm can be reduced or abolished without any loss of voluntary muscle response.

This preparation of curare contains 3 per cent d-tubocurarine in a mixture of 4.8 per cent wax in peanut oil (175 units of standard curare per cubic centimeter of suspension). This product has been injected intramuscularly and has resulted in prolonged curare action, lasting from twenty-four hours to more than one hundred and twenty hours in some cases. The dosage has been carefully adjusted, with a low initial dose and increase of the dose gradually at intervals of twenty-four to forty-eight hours until muscular relaxation occurs. Subsequent doses are then administered at whatever interval (usually seventy-two to ninety-six hours) subjective or objective evidence of muscle spasm begins to reappear. Dosage has been an individual problem and is related to the degree of motor acceleration rather than to age or body weight.[3] Dosage is lowest in conditions (muscle spasm) where the degree of motor acceleration is the least. As this drug is potentially dangerous (because we are establishing a depot in the body of about twice the normal therapeutic dose of the drug), we have observed certain precautions to prevent toxicity:

1. Begin with a conservative initial dose and increase gradually at intervals of not less than twenty-four hours until muscular relaxation is obtained.

2. Use of dry heat in melting the suspension (and shaking vigorously to insure thorough mixing) and use of dry needle

From the University of Buffalo Medical School.
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1. Schlesinger, E. B.: Use of Curare in Oil in Treatment of Spasticity Following Injury of the Spinal Cord, Arch. Neurol & Psychiat. **55**: 530-534 (May) 1946.
2. Schlesinger, E. B., and Ragan, C.: 'Muscle Spasm" in Acute Low Back Pain and Similar Syndromes, Am. J. Med. **1**: 621-627 (Dec.) 1946.
3. Schlesinger, E. B.: Recent Advances in the Use of Curare in Clinical Practice, Bull. New York Acad. Med. **22**: 520-529 (Oct.) 1946.

and syringe in administering the drug, to prevent introduction of moisture into the product.

3. Inject the drug intramuscularly in one site only and do not massage the site of injection.

4. Initial determination of dosage in the hospital where patient's activity can be restricted and observation is possible for eight hours after injection.

5. Discard the product if it shows signs of fluidity or separation at room temperature.

6. Use of this drug is contraindicated when there is evidence of respiratory disease, renal disease, hepatic disease or myasthenia gravis.

If toxicity should result despite these precautions, injection of 1 to 2 cc. of neostigmine (prostigmin®) (1:2,000), which is very effective as a myoneural antagonist, will relieve mild toxic symptoms. In cases of prolonged or serious toxicity (respiratory difficulty), further injection of neostigmine is not beneficial and injections of ephedrine and/or ergotamine tartrate should be administered;[4] an intratracheal airway should be inserted, and artificial respiration and supportive measures should be administered. Ice packs to chill the site of injection will delay further absorption.

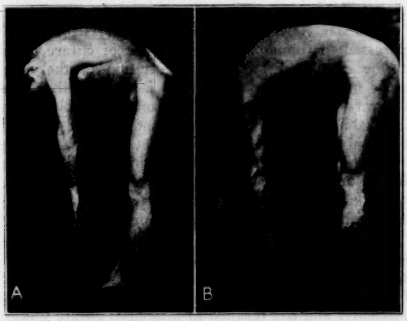


Fig. 1 (case 1).—Early rheumatoid spondylitis. *A*, photograph demonstrating the maximum range of motion before d-tubocurarine therapy. *B*, photograph showing the increased range of motion after the fourth injection of d-tubocurarine.

However, if the aforementioned precautions are observed, we believe that there will be no serious toxicity. Over two hundred injections were administered to this group of 6 patients with rheumatoid spondylitis, and only two mild reactions (blurring of vision, diplopia) were encountered. No treatment was required.

D-tubocurarine chloride in oil-wax suspension was employed in this group of 6 patients, when the usual treatment regimen for rheumatoid spondylitis (roentgen therapy, physical therapy, spinal supports, bed rest and postural training) failed to relieve their pain, muscle spasm, limited motion and flexion deformity of the spine. Spasm of the extensor (paravertebral) muscles and the muscles of the thighs was an outstanding observation in all 6 patients, and 3 patients had significant spasm of the flexor muscles of the spine. To evaluate the results objectively as well as subjectively, measurements of the range of motion, photographs and electromyographic studies were made before and after administration of d-tubocurarine. The electromyograph measures the electrical activity of the muscle. A normal muscle at rest shows no evidence of electrical activity, but a muscle in spasm exhibits "bursts" of abnormal electrical activity. Needle electrodes were inserted into various muscles, especially the erector spinae group, and in some cases into the muscles of the thigh (hamstring, quadriceps, adductor). After d-tubocurarine administration, the electromyographs showed a decided diminution of the abnormal "bursts" of electrical activity.

Three of the 6 patients treated had relatively early disease (involvement of the lower part of the spine only), 2 patients had moderately advanced disease (involvement of the entire spine, but no ligamentous calcification or ankylosis) and 1 patient had far advanced disease (typical "bamboo" spine, pronounced destructive arthritis of hip joints and a range of only 10 per cent motion of the knee joints). Abstracts of the histories of the 6 patients are reported in order of severity.

## REPORT OF CASES

CASE 1.—J. Z., a white boy aged 19, complained of gradually increasing pain and limitation of motion of the lower part of the back for about one year. Previous treatment, consisting of sacroiliac support, roentgen therapy, postural exercises and extensive physical therapy, had not relieved the pain or limited motion of his spine. Physical examination revealed flattening of the normal lumbar curve, loss of 30 per cent motion of the lumbosacral part of the spine in all directions, pronounced spasm of erector spinae and hamstring muscles and considerable pain in the lower part of the back on motion. Roentgenologic examination showed haziness and narrowing of the sacroiliac joints and similar changes in the apophyseal joints of the lower lumbar vertebrae. There was definite evidence of abnormal motor activity on the electromyograph tracings, obtained with needle electrodes in the erector spinae and hamstring muscles. D-tubocurarine was administered, beginning with an initial dose of 0.75 cc. intramuscularly and repeated at twenty-four to forty-eight hour intervals for six doses. After the second injection, the dose was increased to 1.0 cc. (175 units). Following the fourth injection, this patient was able to touch his toes with his finger tips and there was only slight discomfort in the lower part of the back. There was a decided decrease in the degree of muscle spasm at this time. The fifth injection was increased to 1.25 cc., and after this injection the patient complained of blurring of vision, diplopia and a sensation of flushing in the face and head. No treatment was administered since the complaints were very mild. At this time, the patient had a full range of motion of his spine and there was no evidence of muscle spasm either on clinical or electromyographic examination. Dosage was maintained at 1.0 cc. at intervals of four days, for ten more injections. As the patient continued to have a full range of motion of the spine, without pain or muscle spasm, it was decided to discontinue treatment after fifteen injections. At the time of writing this patient had remained asymptomatic for one year with no further treatment.

CASE 2.—R. L., a white man aged 23, had rheumatoid spondylitis involving the sacroiliac joints and the lumbar part of the spine for three years. In the year prior to examination he had noticed a definite increase in pain and a decided impairment of motion of the spine. Examination of the spine revealed the characteristic loss of the normal lumbar curve, loss of 60 per cent of the motion of the lower part of the spine in all directions, moderate decrease in chest expansion and pronounced spasm of the paravertebral muscles and the muscles of the thighs (quadriceps, hamstrings). Roentgenograms showed well advanced arthritic changes in the sacroiliac and all the lumbar apophyseal joints. Electromyographs were obtained of the lumbar paravertebral muscles and the quadriceps group and showed abnormal motor activity. This patient was treated with the usual regimen (which has been described previously),

4. Koppanyi, T., and Vivino, A. E.: Prevention and Treatment of d-Tubocurarine Poisoning, Science **100**:474 (Nov. 24) 1944.

but experienced only minimal relief of pain and no improvement in the range of motion or the amount of muscle spasm present. After an interval of four months with no change in his symptoms, he was given d-tubocurarine in oil-wax suspension. An initial dose of 0.75 cc. was administered and was increased to 1.25 cc. at forty-eight hour intervals. After the fifth injection there was a definite decrease in the amount of muscle spasm (on clinical and electromyographic study), less pain on motion and a 25 per cent increase in the range of spinal motion. D-tubocurarine therapy was continued in the same dosage (1.25 cc.) at intervals of four to six days until a total of twenty injections was given. At that time, patient had obtained a range of motion 80 per cent of normal and was free of pain and muscle spasm. There was no complaint of toxicity during treatment. At the time of writing he had remained asymptomatic for a year with no other treatment except a Taylor brace.

CASE 3.—A. K., a white man aged 22, had had rheumatoid spondylitis for three years. In the nine months prior to examination, pain in the lower part of the back and left hip had become progressively worse and he had been unable to work. Examination of his spine revealed the lumbar part of the spine to be flat, with loss of 75 per cent normal range of motion, decided impairment of chest expansion, moderately severe pain in the back and left hip region on motion and pronounced spasm of the paravertebral muscles and muscles of the left thigh (quadriceps, adductors). Roentgenograms showed moderately advanced arthritis of the sacroiliac joints, the apophyseal joints of the lumbar part of the spine and mild rheumatoid arthritis of the left hip joint. Since there was little relief of pain, muscle spasm or limited motion after intensive treatment (including bed rest, roentgen therapy, physical therapy and spinal brace), d-tubocurarine therapy was instituted after an interval of three months. The initial dose was 0.5 cc. given intramuscularly; this treatment was repeated at forty-eight hour intervals for four doses. The fifth injection was increased to 0.75 cc. and was given every three days for six doses. At this time, there was a 50 per cent increase in the range of motion of the spine and practically all pain and muscle spasm in the lower part of the back and left thigh were relieved. Injections were repeated at intervals of four to five days for the next five months and then discontinued because he was free of all complaints, except for mild "stiffness and tightness" of the lower part of the back and hip region. This patient received a total of forty-five injections and showed no evidence of tolerance or habituation. The only complaint of toxicity was slight blurring of vision on one occasion, which required no treatment. This patient was able to resume his former occupation after d-tubocurarine therapy was instituted and at the time of reporting had been almost completely asymptomatic for eight months with no treatment except postural exercises and a Taylor brace.

CASE 4.—W. R., a white man aged 41, had had rheumatoid spondylitis for eighteen years. For a year prior to examination there had been a gradual progression of the pain and limited motion of the back and neck and some pain in both hips. Examination revealed decided limitation of motion of the neck and back (20 per cent of normal range of motion), a moderate flexion deformity of the cervical and dorsal parts of the spine and pronounced spasm of the paravertebral muscles of the neck and back. Rotation of both hip joints was limited to 50 per cent, with some pain on rotation and abduction. The quadriceps and adductor muscles of both thighs exhibited a moderate degree of spasm on clinical and electromyographic examination. Roentgenograms showed fusion of both sacroiliac joints, involvement of the intervertebral joints of the entire spine, mild decalcification of the vertebrae and moderate arthritic changes of both hip joints. As this patient had previously been treated with roentgen rays, physical therapy, spinal support and, finally, bed rest, without any improvement of the flexion deformity or muscle spasm and pain, combined neck and leg traction was instituted. Because of the degree of discomfort and the slow progress, traction was discontinued and d-tubocurarine was administered. The initial dose was 0.75 cc. given intramuscularly, and the same dose was given twenty-four hours later. The amount was increased to 1.25 cc. and injection repeated at forty-eight to seventy-two hour intervals. After the fifth injection, it was observed that the patient was able to stand erect and that little spasm of the paravertebral muscles was present. There was little discomfort at this time. Treatment with injections was continued at intervals of three to five days until a total of eighteen doses (1.25 cc.) had been administered. At the conclusion of treatment, this patient was able to stand erect and there was no pain or muscle spasm. There was a moderate increase in the range of motion of the spine (40 per cent normal range of motion). This patient required a Taylor brace, some physical therapy and one subsequent course of roentgen therapy, because of recurrence of a moderate amount of pain, for a period of four weeks. However, at the time of writing there had been no recurrence of the flexion deformity and he had retained

Fig. 2 (case 5).—Moderately advanced rheumatoid spondylitis before treatment. The photographs demonstrate the flexion deformity of the spine, the patient's inability to hold his head erect and the muscle spasm (abdomen).

the improvement in motion. He had been performing his regular occupation, which entailed heavy physical exertion, with minimal discomfort for a year.

CASE 5.—C. H., a white man aged 24, had had rheumatoid spondylitis for five years prior to examination. There had been continuous progression of the disease with involvement of the entire spine, thorax and right hip. There had been increasingly severe pain in the back, neck, chest and right hip; progressive loss of motion of the neck and back; loss of chest expansion, and loss of strength and 40 pounds (18 Kg.) in weight. Examination revealed the dorsolumbar part of the spine to be rigid and decided restriction of all motions of the neck (only 20 per cent normal range of motion of the neck). There was a pronounced flexion deformity of the cervical and dorsal part of the spine and practically no chest expansion. One of the outstanding observations on examination was the

very pronounced spasm of the muscles of the neck, spine, thighs and the abdomen. The electromyograph showed decidedly abnormal motor activity when needle electrodes were inserted into the neck, back and thigh muscles. Roentgenograms revealed typical well advanced involvement of the sacroiliac joints and the entire spine and beginning calcification of the longitudinal spinal ligaments. This patient had been treated several times in the hospital, with an intensive regimen consisting of body casts, traction, physical therapy, roentgen therapy, postural exercises, prolonged bed rest, neostigmine (prostigmin®) and procaine hydrochloride injections, without relief of the pain, muscle spasm or flexion deformity. Treatment with d-tubocurarine in oil and wax was begun with an initial dose of 0.75 cc., which was subsequently increased to 1.25 cc. given at intervals of twenty-four to forty-eight hours. After the

Fig. 3 (case 5).—Photographs of the patient after he had received the seventh injection of d-tubocurarine. They demonstrate the improvement in posture, correction of the flexion deformity of the spine, the patient's ability to hold his head erect and relaxation of abdominal muscles.

fourth injection the patient felt "relaxed" and more comfortable, and after the seventh injection it was noted that he was able to stand more erect and was able for the first time to extend the cervical part of the spine and hold his head erect. Injections were continued at intervals of seventy-two hours for the next month and then were administered every five to seven days for five months, during which time the patient could stand erect with no discomfort and wore a Taylor brace. There had been a 15 per cent increase in the range of motion of the neck and spine. At this time, patient voluntarily discarded his brace and discontinued the injections because he felt well. However, he soon suffered a relapse, with a return of pain, muscle spasm and flexion deformity. He was hospitalized again, and treatment with d-tubocurarine injections was reinstituted, with prompt relief of the pain, muscle spasm and flexion deformity; an intensive program of physical therapy and muscle-building exercises was started. Improvement was maintained, and the d-tubocurarine therapy was discontinued after he had received a total of sixty injections with no evidence of toxicity or habituation. He required no further therapy, except for the physical therapy, postural exercises and Taylor brace.

Case 6.—J. A., a white man aged 34, had had a progressive form of rheumatoid spondylitis for twelve years, involving the entire spine, hips, shoulders, thorax and knees, despite all treatment. In 1945, ankylosis of the neck, spine and hip joints was practically complete, and the patient had been confined to bed for the previous two years. Examination revealed a rigid back and neck; no motion in either hip joint could be obtained; severe spasm of the muscles of the back and thighs was present, and any attempt to produce movement of the knee or hip joints was extremely painful. Roentgenograms showed a typical "bamboo" spine and severe arthritis of both hip joints. In the twenty months that he had been hospitalized, the regimen included roentgen therapy, daily physical therapy, prolonged courses of neostigmine (prostigmin®) and procaine hydrochloride injections, with no improvement. He would make an occasional futile attempt to walk with the aid of a walker, but could take only a few steps because of the pain, decided muscle spasm and loss of practically all motion in the hip and knee joints. D-tubocurarine was administered, beginning with 0.75 cc. given intramuscularly, which was subsequently increased to 1.25 cc. at forty-eight hour intervals. After the eighth injection, the patient was able to walk a longer distance, with less discomfort, than for the previous two years. Injections were continued at four to six day intervals for the next four months. The patient continued to improve during this period and was able to walk increasing distances with less discomfort and exhaustion. There was definite evidence of relaxation of the muscles of his back and thighs and an increase of 60 per cent motion of both knee joints during d-tubocurarine therapy. There was only a slight return of motion in the hip joints (15 per cent) and no decrease in the rigidity of the spine. He was able to be out of bed the entire day and was able to walk with little discomfort with the aid of crutches. It was felt by all observers that the rehabilitation of this patient was produced by the d-tubocurarine therapy, as all previous treatment during the hospitalization period of nearly two years had failed to improve his condition in any manner. He received a total of forty-five injections of d-tubocurarine with no evidence of toxicity or habituation and at the time of reporting had maintained this improvement for six months with no subsequent therapy.

## COMMENT

D-tubocurarine in oil and wax suspension was administered to a group of 6 patients with rheumatoid spondylitis, after the usual therapeutic regimen for this disease had failed to produce significant improvement. The results of treatment with d-tubocurarine in these patients were: (1) relief of muscle spasm and pain, (2) increased range of motion and strength, (3) correction of flexion deformity of the spine, (4) evidence of diminished abnormal motor activity on electromyographic study after treatment and (5) ability to take more intensive physical therapy and postural exercise. This group of patients received more than two hundred injections of this drug with no evidence of habituation and practically no toxicity. This oil-wax suspension of d-tubocurarine produced a prolonged "curare" effect, lasting up to one hundred and twenty hours in some cases.

## SUMMARY

We believe that d-tubocurarine in oil and wax has a definite value as an adjuvant measure in the treatment of rheumatoid spondylitis when the usual regimen of treatment is not successful and when the patient has evidence of significant "muscle spasm."

# Council on Pharmacy and Chemistry

## ORGANOMERCURIAL COMPOUNDS

*A report of the Council, titled "The Bacteriostatic and Bactericidal Actions of Some Mercurial Compounds on Hemolytic Streptococci," by Morton and his co-workers, was published in* THE JOURNAL *Jan. 3, 1948, page 36. This paper concerned the usefulness of organomercurial compounds, and, in an introductory statement, the Council emphasized that their usefulness should be further explored and defined.*

*Subsequently, papers by Dr. John H. Brewer and Dr. H. M. Powell on behalf of mercurochrome® (merbromin) and merthiolate® were published under sponsorship of the Council (*THE JOURNAL, *July 3, 1948, page 858).*

*Later the Council considered and commended to* THE JOURNAL *for publication the paper "Antibacterial Action of Commercial Nitromersol Preparations" by Dr. Hobart W. Cromwell, and the paper "The Action of Blood on Germs Presumably Killed by Antiseptics" by Dr. Lorenzo Banti. These papers and additional comments by the authors have been accepted for publication in the Council column.*

*The Council is gratified by the prompt response to its challenge for objective evidence of the therapeutic usefulness of the bacteriostatic action of the organomercurial compounds.*

*In sum, the replies seem to indicate that this bacteriostatic action may, under some conditions, render bacteria noninfective, but that the results vary in conditions that are only partly controllable, especially in clinical practice. It is pointed out that any reduction of infectivity, even though it be uncertain, is to the advantage of the patient, provided (1) that it more than offsets any direct damage to the tissues by the chemical and (2) that the operator appreciate that such reduction of infectivity does not justify any laxness in surgical technic and that asepsis and gentleness must be observed just as meticulously as if no antiseptic were used.*

*With reference to the paper by Banti, the Council considered that the observation that germicidal action is not merely prevented but actually reversed by blood does not greatly alter the problem, namely, whether the concentrations actually used on and in the body are sufficient to accomplish disinfection without too much toxicity. It is pointed out that this depends on individual conditions that cannot be controlled a priori and that it is still a question of one's giving the patient the benefit of the doubt, provided that the actual success in controlled in vivo experiments are sufficient to leave a reasonable doubt.*

*The Council feels that the papers on this subject published under its auspices do not represent a final answer to its challenge.*

AUSTIN SMITH, M.D., *Secretary.*

## ANTIBACTERIAL ACTION OF COMMERCIAL NITROMERSOL PREPARATIONS

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Morton, North and Engley,[1] in a report of their studies of the effect of three mercurials, including nitromersol (metaphen®), on pathogenic streptococci, concluded that the aqueous solutions of these mercurials as marketed "possess many shortcomings as disinfectants." This report, with the accompanying comments from the Council on Pharmacy and Chemistry of the American Medical Association, gives the reader the impression that all commercial mercurial preparations are of doubtful value as antibacterial agents. This impression is evident in the semipopular report in *Science News Letter* for Jan. 10, 1948.[2] Their experiments with nitromersol will be discussed later in this paper.

The purpose of this communication is to present experimental data on the antibacterial action of two market preparations, metaphen® disinfecting solution and tincture of metaphen,® 1 to 200, which are the nitromersol products most widely used. Metaphen® disinfecting solution contains 1 part nitromersol dissolved in 2,500 parts of water containing sodium hydroxide U. S. P., 0.81 Gm.; sodium carbonate, monohydrated, 12.5 Gm.; ethylene glycol, 500 Gm., and benzyl alcohol, 100 Gm. It is recommended for the cold disinfection of dental and surgical instruments. Metaphen® tincture, 1 to 200, contains 0.5 Gm. of nitromersol in 100 cc. of an alkalinized solvent consisting of alcohol, 50 per cent; acetone, 10 per cent, and water. For preoperative preparation of the skin a certified dye is added to mark the area of application, but for other topical applications the tincture without dye is available.

The experimental data presented here have been selected from studies on mercurial antiseptics made in the Abbott laboratories over the past five years and, therefore, not designed specifically to meet the challenge of the Council. However, the data on metaphen® disinfecting solution were accepted in January 1946 by the Council on Pharmacy and Chemistry of the American Medical Association as evidence sufficient to include this preparation in "New and Nonofficial Remedies."

### METAPHEN® DISINFECTING SOLUTION

Morton and his co-workers,[1] Brewer[3] and Powell[4] have shown that in vitro culturing in thioglycollate broth approximates in sensitivity the animal inoculation method of testing viability of mercurial-treated bacteria. In the Abbott tests of metaphen® disinfecting solution thioglycollate broth was used for subculture; otherwise the method was the same as described by Ruehle and Brewer.[5] To 5 cc. of the test solution at 20 C. was added 0.5 cc. of a twenty-four hour culture of the test organism, mixed by shaking. At suitable intervals one 4 mm. loopful of the mixture was planted into 10 cc. of thioglycollate broth and mixed. The cultures were incubated at 37 C. at least four days before final reading of the results.

Table 2 shows the results of sixteen tests of metaphen® disinfecting solution against Staphylococcus aureus, F.D.A. strain 209, with thioglycollate broth, Linden formula, the same as Morton and his associates used. Complete killing was obtained in all trials in five minutes' exposure at 20 C., and in 13 of the 16 trials no growth was obtained after three minutes' exposure.

In table 1 is the summary of tests against two other strains of Staphylococcus, three strains of Streptococcus, one strain of Monilia, a pathogenic yeast, and two strains of Escherichia coli. The broth used for subculture was freshly prepared nutrient broth containing 0.1 per cent sodium thioglycollate. This was used because some of the organisms grew more readily in this than in the Linden formula. Of a total of 128 subcultures made at various time intervals in this series of tests, only two produced growth, one of a Staphylococcus after one minute exposure at 20 C. and one of a hemolytic Streptococcus after two minutes' exposure.

These results indicate that metaphen® disinfecting solution has a definite and rapid lethal action against the organisms tested.

From the Abbott Research Laboratories.

1. Morton, H. E., North, L. L., and Engley, E. B., Jr.: The Bacteriostatic and Bactericidal Actions of Some Mercurial Compounds on Hemolytic Streptococci, J. A. M. A. **136**: 37-41 (Jan. 3) 1948.
2. Science News Letter **53**: 29 (Jan. 10) 1948.
3. Brewer, J. H.: Reduction of Infectivity of Certain Pathogenic Bacteria by "Mercurochrome," J. A. M. A. **137**: 858-861 (July 3) 1948.
4. Powell, H. M.: Antibacterial Action of "Merthiolate" Against Hemolytic Streptococci, J. A. M. A. **137**: 862-866 (July 3) 1948.
5. Ruehle, G. L. A., and Brewer, C. M.: United States Food and Drug Administration Methods of Testing Antiseptics and Disinfectants, Circular 198, United States Department of Agriculture, December, 1931.

### TINCTURE METAPHEN,* 1 TO 200

Since tincture metaphen,* 1 to 200, is intended primarily for use in preoperative disinfection of skin, it was tested by the in vivo method of Nungester and Kempf,[6] with a Pneumococcus type 1, and a hemolytic Streptococcus, strain C 203. In this procedure white mice were used as test animals. The tail of the mouse was contaminated with an undiluted blood-broth culture of the organism and, after it was dry, treated with the chemical solution. After a suitable interval, three minutes in these experiments, about 8 mm. of the distal portion of the tail was snipped off and planted in the abdomen of the same mouse. If the mouse survived seven days without visible evidence of infection, the skin was considered "disinfected." Conversely, if the mouse died with morphologically typical organisms in the heart's blood, the skin was not disinfected. Those that died without typical organisms in the blood were very few, and were not included in the summary. The virulence of the test organisms varied somewhat but averaged about 5,000,000 lethal doses per cubic centimeter for 20 Gm. mice for the Pneumococcus blood-broth cultures and about 1,000,000 lethal doses per cubic centimeter for the Streptococcus cultures.

TABLE 1.—*Results of Tests of Metaphen* Disinfecting Solution Against Various Micro-Organisms at 20 C. with Thioglycollate Broth for Subculture*

| | Exposure (Minutes) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 5 |
| **Staphylococcus aureus (2 strains)** | | | | |
| Positive cultures | 1 | 0 | 0 | 0 |
| Negative cultures | 7 | 8 | 8 | 8 |
| **Hemolytic streptococcus (2 strains)** | | | | |
| Positive cultures | 0 | 1 | 0 | 0 |
| Negative cultures | 8 | 7 | 8 | 8 |
| **Viridans streptococcus (1 strain)** | | | | |
| Positive cultures | 0 | 0 | 0 | 0 |
| Negative cultures | 4 | 4 | 4 | 4 |
| **Monilia albicans (1 strain)** | | | | |
| Positive cultures | 0 | 0 | 0 | 0 |
| Negative cultures | 4 | 4 | 4 | 4 |
| **Escherichia coli (2 strains)** | | | | |
| Positive cultures | 0 | 0 | 0 | 0 |
| Negative cultures | 8 | 8 | 8 | 8 |

In table 3 are recorded the results of tests of metaphen* tincture in comparison with two competitive mercurial tinctures, M2 and M3, and three tinctures of quaternary ammonium salts, Q1, Q2 and Q3, and the vehicle alone, consisting of alcohol 50 per cent, acetone 10 per cent and water.

None of these preparations was 100 per cent effective, which is not surprising since this test is much severer than would be encountered in the usual operative procedures. The different market preparations varied considerably, which indicates that neither the mercurials nor the quaternary ammonium compounds should be approved or condemned as a class, but that the individual market preparations should be evaluated as nearly as possible for the purpose for which they are intended. Tincture metaphen,* 1 to 200, compared favorably with other products tested and was much better than the vehicle consisting of alcohol, acetone and water. With the Pneumococcus, it proved effective in 59 per cent of thirty-seven trials and, with Streptococcus C 203 in 95 per cent of forty-two trials. The nearest approach to this was a tincture of a quaternary ammonium compound, Q1, which showed 54 per cent effectiveness against the Pneumococcus and 95 per cent against Streptococcus C 203. Tincture metaphen* was at least equal to the Q1 preparation in skin disinfection and definitely superior to the other commercial preparations.

6. Nungester, W. J., and Kempf, A. H.: An "Infection-Prevention" Test for the Evaluation of Skin Disinfectants, J. Infect. Dis. **71**: 174-178 (Sept.-Oct.) 1942.

### COMMENT

The Council on Pharmacy and Chemistry of the American Medical Association has invited the manufacturers of mercurial disinfectants to present evidence of the effectiveness of their products. The experimental work of Morton and his associates dealt with aqueous mercurial solutions only, and their results are in agreement with the known characteristics of such substances, namely, their high bacteriostatic potency and slow lethal action against gram-positive organisms. In addition to the usual in vitro disinfectant testing with subcultures in thioglycollate broth, mixtures of the mercurial solutions and organisms were injected into white mice to determine infectivity of the treated bacteria. They found that the equivalent of 100,000 lethal doses of Streptococcus pyogenes, strain C 203 M, after ten minutes' exposure of 0.1 cc. of aqueous metaphen,* 1 to 500 solution, produced fatal infection in only 3 of 8 mice inoculated. In other words, 100,000 lethal doses were reduced to approximately 1 by this treatment. These results indicate that aqueous metaphen,* 1 to 500 solution, does have some merit as a disinfectant, although, admittedly, the authors do not define its field of usefulness.

In common with most known antiseptic chemicals, the activity of metaphen* is greatly reduced by contact with tissues and body fluids. A concentration lethal to unprotected organisms in culture might, in the presence of serum, blood or pus, be only bacteriostatic, particularly against gram-positive organisms. Whether the mixture would be bactericidal, bacteriostatic or entirely ineffective would depend largely on the amount of such organic matter in relation to the concentration of the mercurial. The high bacteriostatic potency should be an advantage in treatment of superficial wounds and abrasions with metaphen,* in comparison with other chemicals which are not highly bacteriostatic and which are equally reduced in activity by tissues and body fluids.

TABLE 2.—*Results of Tests of Metaphen* Disinfecting Solution Against Staphylococcus Aureus FDA Strain 209 at 20 C. with Thioglycollate Broth for Subculture*

| | Exposure (Minutes) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 5 |
| Positive cultures | 16 | 11 | 3 | 0 |
| Negative cultures | 0 | 5 | 13 | 16 |

TABLE 3.—*Results of Skin Disinfection of Mice by the Nungester and Kempf Method (Test Organisms Pneumococcus Type 1 and Streptococcus C 203)*

| | Pneumococcus Type 1 | | | Streptococcus C 203 | | |
|---|---|---|---|---|---|---|
| Test Organism Mice | Used | Survived | Percentage | Used | Survived | Percentage |
| Tincture "metaphen" | 37 | 22 | 59 | 42 | 40 | 95 |
| Tincture M2 | 28 | 5 | 18 | 15 | 0 | 0 |
| Tincture M3 | 37 | 8 | 22 | 36 | 32 | 86 |
| Tincture Q1 | 37 | 21 | 54 | 37 | 35 | 95 |
| Tincture Q2 | 37 | 11 | 30 | 36 | 27 | 75 |
| Tincture Q3 | 37 | 6 | 16 | 36 | 15 | 42 |
| Alcohol-acetone-water | 21 | 2 | 10 | 24 | 3 | 12 |
| Controls (inoculated but untreated) | 22 | 0 | 0 | 23 | 0 | 0 |

Aqueous metaphen,® 1 to 500, is recommended by the manufacturers only for the irrigation of infected wounds and the preparation of wet dressings, conditions which assure prolonged contact.

The results of Morton's work with aqueous solutions cannot properly be used in estimation of other mercurial preparations containing substances which may have a potentiating effect on the mercurial, or an additive effect, or otherwise may enhance the germicidal properties of the solution. Since metaphen® disinfecting solution and tincture metaphen,® 1 to 200, do contain such substances, this experimental evidence of their effectiveness is presented.

Metaphen® disinfecting solution has proved rapidly germicidal against several genera of pathogenic or potentially pathogenic organisms, in tests with subcultures in thioglycollate broth. For this solution, germicidal tests in presence of serum or blood would be unimportant, since the instruments to be disinfected should first be thoroughly cleaned.

Although tincture metaphen,® 1 to 200, tested by the rather severe in vivo method of Nungester and Kempf, did not prove 100 per cent effective, it did compare very favorably as a skin disinfectant with five other commercial preparations recommended for that purpose, two tinctures of mercurials and three tinctures of quaternary ammonium salts. It was definitely better than all the others, except possibly one of the quaternary ammonium salts, to which it was at least equal in effectiveness.

SUMMARY

Metaphen® (nitromersol) disinfecting solution has been tested for its germicidal action in vitro against three strains of Staphylococcus, three strains of Streptococcus, one strain of Monilia, a pathogenic yeast, and two strains of Escherichia coli, with thioglycollate broth for subculture. By this method the FDA 209 strain of Staphylococcus aureus was always killed in five minutes or less at 20 C. in a total of 16 trials. More rapid killing was obtained with the other organisms.

Tincture metaphen,® 1 to 200, has been tested for skin disinfection by the in vivo method of Nungester and Kempf in comparison with five other commercial tinctures offered for that purpose, two mercurials and three quaternary ammonium compounds. By this rather severe method, tincture metaphen,® 1 to 200, was found definitely superior to all the other preparations, except possibly one of the three quaternary ammonium compounds, to which it was at least equal in value.

The experiments of Morton and his associates on the disinfectant action of aqueous metaphen,® 1 to 500, solution, are discussed.

*This paper was submitted to Dr. Morton, who, with his associates, wrote the original report and made the following comment:*

"The report by Morton, North and Engley (THE JOURNAL, Jan. 3, 1948, page 37) dealt only with the aqueous solutions of metaphen,® merthiolate® and mercurochrome.® The replies by Dr. Brewer on mercurochrome® and by Dr. Powell on merthiolate® (THE JOURNAL, July 3, 1948, page 858) likewise, have dealt with aqueous solutions. This report by Dr. Cromwell presents no data on the aqueous solution of metaphen.® In a letter to the editor of *The Bulletin of the American Society of Hospital Pharmacists* (that journal, pages 98 and 132, May-June issue, 1948) Edgar B. Carter, Executive Director of Research, Abbott Laboratories, made the statement, 'We have known for many years that, in an aqueous menstruum, a 1-500 dilution of metaphen® is right at the border of the killing range against Gram-positive cocci.' The label on metaphen,® 1 : 500 solution, carries the statement, 'An organic mercury compound of high antiseptic potency. . . .' Our paper showed that growth of a test organism, after its exposure to a mercurial compound in thioglycollate medium, paralleled infectivity of the organism for the animal body. That has been adequately confirmed. If the micro-organisms are not killed, sepsis may not be prevented.

"Dr. Cromwell in his comments stated that the manufacturers recommend aqueous metaphen,® 1 to 500, only for the irrigation of infected wounds and the preparation of wet dressings, conditions which assure prolonged contact. In addition to these, it is also recommended as a first aid measure on the label.

"If the menstruum has a potentiating effect on the mercurial, such action should be demonstrated experimentally and so indicated in descriptive literature (as for example, 'New and Nonofficial Remedies') and on the label, so that users of the compounds do not get the impression that the mercurial, per se, or any other one compound in the product is the sole active ingredient. It is regrettable that Dr. Cromwell did not include in his results in tables 1 and 2 the action of the menstruum in the metaphen® disinfecting solution on the test organisms as he did with his work on the action of tincture metaphen® listed in table 3."

*These comments were submitted to Dr. Cromwell, who replied in part as follows:*

"The referees' report makes a point of the omission from this paper of data on the aqueous solution of metaphen.® I did not attempt to repeat the work of Morton, North and Engley on aqueous solutions because their experiments seemed to be adequate, and the results in agreement with the known antibacterial characteristics of mercurials, i. e., slow germicidal action against gram-positive organisms, and a powerful and sustained bacteriostatic effect.

"The report implies that the use on the package label of the expression 'high antiseptic potency' is an exaggerated description of the antibacterial properties of metaphen,® 1 to 500 solution. Possibly the term 'bacteriostatic' is more exact than 'antiseptic,' but, according to my understanding of the term, this solution is antiseptic when used, as recommended by the manufacturer, under conditions assuring prolonged contact.

"With reference to our tests on metaphen® disinfecting solution, it did not seem important at the time to test the menstruum alone without the metaphen.® Obviously, the menstruum either potentiates the action of the mercurial or has an additive effect, because it has been amply demonstrated that aqueous metaphen® solution alone does not kill gram-positive organisms rapidly, while the complete solution proved rapidly germicidal. Benzyl alcohol, 4 per cent solution, is a germicide, and it is listed on the label of metaphen® disinfecting solution as one of the active ingredients, although we may not understand completely the mechanism of its action in relation to metaphen® in the solution.

"Thank you for giving me the opportunity to read the referees' report and to make these comments."

*Dr. Cromwell's comments were referred to Dr. Morton who replied that he had no further comment to offer.*

*Subsequently the following paper by Lorenzo Banti, Instituto Biologico Argentino, Florencio Varela, F.C.S., Argentina, was received by the Council's office:*

# THE ACTION OF BLOOD ON GERMS PRESUMABLY KILLED BY ANTISEPTICS

LORENZO BANTI
Florencio Varela, F.C.S., Argentina

A recent report by Morton, North and Engley[1] has opened an interesting controversy about the antibacterial action of some mercurial compounds. Attention has been called by these authors to the fact, already known,[2] that bacteria believed to be killed, because of their failure to grow in common culture mediums, may be "resuscitated" by being transferred to Linden's thioglycollate broth; they have found, moreover, that hemolytic streptococci susceptible to revival by thioglycollate are also able to infect and cause the death of mice when injected intraperitoneally into them. As the result of these findings the scope of usefulness of these mercurial compounds as disinfectants would seem to be limited. Brewer[3] and Powell[4] later strove to prove that the mercurials mercurochrome® and merthiolate® possess, under certain conditions, a definite antibacterial action; but the validity of their conclusions is still open to doubt.

TABLE 1.—*Results of 0.2 Cc. of Culture of Staph. Aureus in 4.8 Cc. of Antiseptic Solution*

| Material | Time | Broth | Thioglycollate Medium | Blood Broth |
|---|---|---|---|---|
| Mercuric chloride, 1 o/oo * | 3 min. | + | + | + |
| | 12 min. | ± | + | + |
| | 25 min. | − | ± | ± |
| | 60 min. | − | ± | ± |
| "Merthiolate," 0.96 o/oo | 3 min. | − | + | + |
| | 12 min. | − | + | + |
| | 60 min. | − | + | + |
| | 20 hr. | − | + | + |
| "Mercurochrome," 2% | 12 min. | − | + | + |
| | 60 min. | − | + | + |
| Hypochlorite solution, 5.9 o/oo active chlorine ("antibacter") | | | | |
| Diluted 1:11.2, 0.53 o/oo active chlorine | 3 min. | − | − | + |
| Diluted 1:8, 0.75 o/oo active chlorine | 3 min. | − | − | − |
| Diluted 1:5.9, 1.00 o/oo active chlorine | 3 min. | − | − | − |
| Chloramine T, 0.5 o/oo | 3 min. | ± | + | + |
| 1 o/oo | 3 min. | − | ± | + |
| 2 o/oo | 3 min. | − | ± | ± |
| 4 o/oo | 3 min. | − | − | − |
| Octadecyldimethylbenzylammonium chloride 0.025 o/oo | 3 min. | + | + | + |
| 0.050 o/oo | 3 min. | − | − | + |
| 0.100 o/oo | 3 min. | − | − | − |
| Phenol, 1.00% | 3 min. | ± | + | + |
| 1.26% | 3 min. | ± | ± | ± |
| 1.50% | 3 min. | − | − | − |

* o/oo is parts per thousand.

It is already known that germs apparently killed by antiseptics other than mercurials, as phenol, hypochlorites and the like, may be revived by special methods of cultivation. Reference may be made to the papers by Flett, Haring, Guiteras and Shapiro,[5] Mudge and Smith,[6] McIlwain[7] and Valko and DuBois.[8] The first of these papers, for instance, shows that ferric chloride or activated charcoal may counteract the effects of the exposure of germs to phenol, although this possibility is limited to concentrations of the antiseptic very little greater than those that are normally considered fatal. It appears that the antiseptic previously bound by the bacterial cells may be removed by chemical or physical action, leaving the germs free from the drug that would ultimately have led to their death. As most tissues and fluids of the animal body contain components chemically similar to components of bacterial cells, it is logical to presume that they will be able to combine similarly with the antiseptics and might even be able to remove the small amounts of them that have been bound by the germs. My co-workers and I thought, therefore, that it would be interesting to investigate this possibility, and we decided to begin by investigating whether, and to what extent, blood might have an effect similar to that of thioglycollate in reviving germs apparently killed by mercurial compounds and, also, whether this action was limited to mercurials or whether it could be observed also with other known antiseptics.

## EXPERIMENTAL

The organisms selected for our experiments were twenty-four hour broth cultures of Staphylococcus aureus, a germ that is extensively used in performing disinfection tests. For antiseptics we selected: mercuric chloride; two organomercurial compounds, mercurochrome® and merthiolate®; two chlorine antiseptics, hypochlorite and chloramine T; one quaternary ammonium detergent, octadecyldimethylammonium chloride, and phenol.

As the number of germs used and the amount of organic matter present may alter considerably the results in disinfection tests, we performed two series of experiments. In one of them we added 0.2 cc. of the culture of Staph. aureus to 4.8 cc. of the antiseptic solution in each test tube; in the other one we added 1 loopful of the same culture to 5 cc. of the antiseptic solution. At intervals we transferred 1 loopful of the mixture of culture and germicide to each of three tubes containing about 10 cc. of one of the following culture mediums: 2 per cent peptone broth, Linden's fluid thioglycollate medium and blood broth containing 10 per cent fresh defibrinated horse blood in 2 per cent peptone broth. The broth was prepared in both instances by decoction of horse meat 1:2. The three tubes were always inoculated from the same culture-antiseptic mixture tube in the order mentioned, so that the intervals corresponding to the thioglycollate and to blood subcultures were, respectively, about 35″ and 70″ greater than the interval corresponding to the broth subculture. The growth in the blood broth tubes was not always evident by simple inspection, so that a microscopic control was often necessary; microscopic controls were also generally performed on most of the critical tubes of all mediums.

The hypochlorite solution used was a proprietary product called antibacter®; it contained 5.9 parts per thousand of active chlorine.

From the Research Laboratory of the Instituto Biologico Argentino, Florencio Varela, F.C.S., Argentina.

1. Morton, H. E.; North, L. L., and Engley, F. B.: The Bacteriostatic and Bactericidal Actions of Some Mercurial Compounds on Hemolytic Streptococci, J. A. M. A. **136**: 37-41 (Jan. 3) 1948.

2. Heinemann, B.: A Comparison of Methods Used for Evaluating the Bactericidal Properties of Mercurial Compounds, J. Am. Pharm. A. (Scient. Ed.) **32**: 298-301 (Nov.) 1943.

3. Brewer, J. H.: Reduction of Infectivity of Certain Pathogenic Bacteria by "Mercurochrome," J. A. M. A. **137**: 858-861 (July 3) 1948.

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## RESULTS

The results of the first series of experiments are summarized in table 1, those of the second series are summarized in table 2. As most of the experiments were repeated twice, we marked with ± those that showed growth in one instance and did not in the other one.

Our experiments show that for most of the antiseptics the subcultures in blood broth definitely favor the growth of germs that already fail to grow in peptone broth or even in thioglycollate medium. The thioglycollate medium is possibly more active with mercurial antiseptics than blood broth, as is shown by the results with mercurochrome* in table 2; better results may perhaps be attained with a greater amount of blood. It is to be mentioned that blood broth must be freshly prepared, as it seems to lose some of its properties after a few days.

The germs selected for our experiments did not allow us to check our results by animal inoculation, as was done by Morton, North and Engley, who experimented with a virulent Streptococcus strain; but we have been able to show the effect of blood as an antidote on the antibacterial action of most antiseptics. This fact seems to us particularly important, as blood is always present in tissues where an infectious process may develop, so that it will always be available to germs that have not been permanently damaged by the antiseptic.

For mercurochrome* and merthiolate,* under the conditions of our experiments, the bactericidal properties were practically nonexistent when germs exposed to their action were subcultured in blood broth or thioglycollate medium. Even mercuric chloride is shown to be a poor disinfectant. For the remaining drugs the really bactericidal concentrations were mostly found to be higher than might have been expected from the subcultures in peptone broth; but they compare favorably with those that are generally used in practice.

Experiments not recorded here tend to show that serum has also an action similar to defibrinated blood, although it is generally less effective. It is probable that most body tissues exert a more or less similar action.

## COMMENT

In 1937 Marshall and Hrenoff [9] pointed out that the action of an antiseptic may be represented by a graphic, which they called antibacterial, spectrum, that shows the properties of a given substance. In this spectrum there is a toxic zone, where the concentration of the antiseptic is too high to be of practical usefulness; a germicidal zone; a bacteriostatic zone, and mostly a zone where, at low concentrations of the drug, it will exert on the germs a stimulating action.

The concentration of the antiseptic is generally considered bacteriostatic when it will prevent the multiplication of the germs, leaving them so far undamaged that they will be able to grow if they are transferred to a medium that does not contain the antiseptic and is able to support their growth. At such concentrations the antiseptic, if harmless, may be used as a preservative.

Bactericidal concentrations are generally much higher, but it is now found that concentrations that would be considered bactericidal if assayed by the phenol coefficient method, that is by the usual method, are not really such in many instances; the germs that seemed to have been killed may be revived if appropriately treated. Between the bacteriostatic and the bactericidal zone there is a zone, that had scarcely been considered until now, where the action of the antiseptic is reversible. At concentrations corresponding to this zone the germs will absorb enough of the drug to prevent their growth when they are transferred to a medium that would be normally able to support it; but if transferred to a suitable medium the germs will again be able to reproduce. The concept of reversibility seems to me particularly appropriate, as its mechanism appears to be similar to the reversibility of a chemical reaction; there is even here a mass action as the revival of the germs is obtained by the addition of substances capable of combining with the antiseptic; the conditions that had been attained in the culture-antiseptic mixture are reversed when the germs are transferred to a medium that is able to remove and bind the drug that the cells had previously absorbed.

In practice the limits of this reversibility zone may be restricted and distant enough from the toxic zone so as to leave still a margin of safety; the drug will still be useful as a bactericide. But it may happen that the reversibility zone is so wide that it overlaps the toxic zone; the drug will then have no use as a bactericide.

TABLE 2.—*One Loopful of Culture of Staph. Aureus in 5 Cc. of Antiseptic Solution*

| Material | Time | Broth | Thioglycollate Medium | Blood Broth |
|---|---|---|---|---|
| "Merthiolate," 1 o/oo * | 3 min. | − | + | + |
| | 12 min. | − | + | + |
| | 60 min. | − | + | + |
| | 20 hr. | − | + | + |
| "Mercurochrome," 2% | 3 min. | + | + | + |
| | 12 min. | − | + | + |
| | 60 min. | − | + | − |
| Hypochlorite solution, 5.9 o/oo act. Cl ("antibacter") | | | | |
| Diluted 1:640, 0.0092 o/oo act. Cl.. | 3 min. | + | + | + |
| Diluted 1:320, 0.0185 o/oo act. Cl.. | 3 min. | ± | + | + |
| Diluted 1:160, 0.0370 o/oo act. Cl.. | 3 min. | − | − | − |
| Diluted 1:80, 0.0740 o/oo act. Cl.. | 3 min. | − | − | − |
| Chloramine T, 0.05 o/oo | 3 min. | + | + | + |
| Chloramine T, 0.10 o/oo | 3 min. | + | + | + |
| Chloramine T, 0.20 o/oo | 3 min. | − | − | − |
| Chloramine T, 0.40 o/oo | 3 min. | − | − | − |

* o/oo is parts per thousand.

As to the controversy about the usefulness of mercurochrome* and merthiolate,* it seems to me that it cannot be solved if these drugs are considered by themselves, that is without comparison with other known antiseptics. The ideal germicide is probably still to be found; there is still some question about the usefulness of germicides in general; but if a germicide has to be used, one should logically resort to those that show higher germicidal properties and a wider safety margin.

## SUMMARY

Blood is able to revive, within certain limits, germs that by ordinary standards would be considered to have been killed by antiseptics. In Marshall and Hrenoff's antibacterial spectrum, between the bacteriostatic and the bactericidal zone, a "reversibility zone" must be inserted, where germs presumably killed may be revived. The extent of this reversibility zone will in part determine the possible usefulness of the drug as a germicide. Mercurial compounds appear, by this standard, to be very poor germicides.

9. Marshall, M. S., and Hrenoff, A. K.: Bacteriostasis, J. Infect. Dis. 61: 42-54 (July-Aug.) 1937.

# Committee on Cosmetics

*The Committee on Cosmetics has authorized publication of the following statement on its rules and procedures. A copy of these rules may be obtained from the Committee office on request.*

AUSTIN SMITH, M.D., *Secretary.*

## STATEMENT BY THE COMMITTEE ON COSMETICS

The Board of Trustees of the American Medical Association recently authorized the formation of a Joint Committee on Cosmetics to study problems relating to medical interest in cosmetics and to effect a better understanding of the usefulness of cosmetics. The members appointed are:

Howard T. Behrman, M.D., Assistant Clinical Professor of Dermatology, New York University.

Morris Fishbein, M.D., Editor, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION and *Hygeia.*

Harry R. Foerster, M.D., Assistant Professor of Dermatology, University of Wisconsin; Associate Professor of Dermatology, Marquette University.

Harry Huber, M.D., 122 South Michigan Ave., Chicago.

A. J. Lehman, M.D., Ph.D., Chief, Division of Pharmacology, Food and Drug Administration.

Mr. Herbert R. Mayes, Editor, *Good Housekeeping Magazine.*

Herbert Rattner, M.D., Associate Professor of Dermatology, Northwestern University School of Medicine.

Austin Smith, M.D., Director, Division of Therapy and Research; Secretary, Council on Pharmacy and Chemistry.

Louis C. Zopf, M.D., Professor of Pharmacy; Chief, Department of Drug Service, College of Pharmacy, State University of Iowa.

The first meeting of the Committee was held Oct. 12, 1948, at which time the immediate objectives of the Committee were defined as follows:

1. A study and classification of currently widely used cosmetics.
2. A study of the claims made for these various preparations.
3. The determination of the safety or harmfulness of cosmetic preparations.
4. The preparation of an outline of cosmetics acceptable to the Committee, and of those it now is unwilling to accept.
5. The preparation of a series of informative articles for the medical profession and the general population. (Hair and Scalp Treatments and Preparations, J. A. M. A. **139**: 840-844 [March 26] 1949; Hair Dyes, *Hygeia* **27**: 318 [May] 1949.)

At a second meeting of the Committee, it was voted that the word "Joint" be dropped from the name of the Committee and that it would be known henceforth as the Committee on Cosmetics and membership increased to include an allergist. At the same time, a seal of acceptance was adopted to be awarded to those cosmetics which meet the requirements of the Committee. In general, the policies in this regard will be similar to other evaluation programs of the Councils in the Division of Therapy and Research.

Manufacturers may now submit their products to the office of the Secretary of the Committee on Cosmetics in conformance with the following official rules.

### Official Rules of the Committee on Cosmetics of the American Medical Association

*Rules Governing the Acceptance of Cosmetics by the Committee*

RULE I—COMPOSITION.—The qualitative and, where possible, the quantitative composition of cosmetics submitted to the Committee must be made known to the Committee. This information will be held in confidence except when it is necessary to reveal the information because of a health problem that arises. Working formulas also will be held in confidence.

RULE II—IDENTIFICATION AND CONTROL.—Suitable procedures for assuring control of the finished product must be supplied to the Committee by the distributor or manufacturer.

RULE III—THERAPEUTIC CLAIMS.—Therapeutic representations normally will not be accepted by the Committee, as such representations normally make the product a drug, which comes within the purview of the Council on Pharmacy and Chemistry. At times, however, there may be exemptions from this rule, such exemptions being determined individually for the submitted items.

RULE IV—ADVERTISING.—Advertising must conform to claims or statements that can be proved by information submitted by the distributor or manufacturer or that are based on common knowledge.

RULE V—NAMES.—Trademark names for cosmetics accepted by the Committee should not be misleading, suggestive of the treatment of disease or its symptoms or in any way capable of influencing the health of the purchaser by deception.

RULE VI—PATENTS AND TRADEMARKS.—If a cosmetic is patented or trademarked, the number of such patents and the name and number of the registered trademarks should be submitted to the Committee.

RULE VII—USELESS ARTICLES.—A preparation will not be accepted by the Committee if it obviously has no value as a cosmetic.

*Outline of Presentation of Submitted Product*

When a product is submitted to the Committee on Cosmetics the interested distributor or manufacturer should supply three (3) trade packages of each item; twelve (12) copies of all labels, instructions and advertising material proposed for the product, and a sample of each ingredient contained in the product.

Also accompanying this material there should be a description in *triplicate* supplying the following:

1. The name of the product, and any synonyms that may be in use.
2. A description of the control procedures that are used to assure a product of the claimed identity, quality and purity.
   (*a*) An analysis of each batch of raw materials.
   (*b*) An outline of a system for checking the exact amounts of the various ingredients that go into each batch.
   (*c*) A description of the record of the lots of raw materials used in each batch.
   (*d*) A statement on the code system for identification of each batch.
3. A definition of the article and its complete formula.
4. A description of the physical properties.
5. A statement of any pharmacologic action that might be expected from any of the ingredients and from the final product.
6. A report from qualified experts on the value of the product for those uses for which it is recommended, provided that it differs from those in common use.
7. A report of toxicologic studies, sufficiently complete to establish the safety of the product when put to its intended use.
8. The numbers of any patents and the names and numbers of any trademarks that may have been assigned to the submitted preparations.
9. A list of the forms and sizes in which the article is made available.
10. Studies on patch tests:
   (*a*) Two hundred to 1,000 subjects (the figure 200 is to be regarded as an absolute minimum).
   (*b*) Method of paired comparisons is desirable, but not required.
   (*c*) Control-old formula of similar nature or usage whenever possible.
   (*d*) Routine 48 hour test with daily readings for three additional days.
   (*e*) Technic: With liquids: Saturate a suitable substance, such as a piece of gauze ½ to 1 inch (1.3 to 2.5 cm.) square, four plys thick; squeeze out excess liquid and apply to normal skin of arm, leg or back; cover with nonwaterproof cellophane 2 inches (5.1 cm.) square and seal with adhesive plaster 3 inches (7.6 cm.) square.

   With powder: Place powder on gauze moistened with water or isotonic sodium chloride solution, and duplicate above.

   With solids: These can be powdered, or, if soluble, they can be dissolved in definite concentrations and tested as above. When the solid is of a resinous character, the solution containing it may be painted on the skin and the solvent allowed to evaporate. The dry

film of resin can be covered with cellophane and adhesive plaster as indicated.

(*f*) Retest in fourteen to twenty-one days following same routine at original sites.

11. Report on usage studies:

(*a*) In a controlled group, preferably on the same subjects used in routine patch test studies.

(*b*) Duplicate conditions of actual usage and on actual sites of expected usage for a period of from two to twelve weeks.

(*c*) It may be advisable to have a control experiment with old cosmetics of similar purpose and/or formula, when claims of superiority are offered or when irritation is a possible factor. Use either on alternate series of subjects or on same subjects dividing body surface (new cosmetics on one side, old cosmetics on other). If no dermatitis occurs in 200 subjects, product is probably safe; if in more than 1, product unsafe. If only 1 case, retest a new series; if 1 or more cases in new series, product is unsafe.

(*d*) It may be advisable to have a trial sale, to be carried out where control or supervision can be maintained. Over a six month period, at least one thousand units should be sold and watched. All sales persons should be instructed to report complaints.

12. The name of the firm that is responsible for the finished article as labeled.

13. The names of the manufacturers of all ingredients contained in the article.

14. A statement of the laboratory and control personnel of the firm responsible for the formulation and control of the product.

In some instances it will be unnecessary to supply in detail all data listed in the Outline of Presentation of Submitted Product, if there is sufficient information available in general knowledge pertaining to the products or their ingredients. However, each submitted product must be given individual consideration.

### Decisions of General Interest

*"Hypoallergenic."*—The committee will permit the use of the term "hypoallergenic" when it is applied to products that will meet the Committee's definition for this term. The Committee has defined "hypoallergenic" to mean that every possible care has been taken in formulation and production to insure minimum instance of allergic reaction. In evaluation of products so labeled, the absence from the formula of common allergens and the special selection and purification of ingredients should be the basic criteria. Manufacturers of hypoallergenic products should be prepared to offer clinical data to support the claim.

*Definition of "Cosmetic."*—For purposes of determining what products come within the purview of the Committee on Cosmetics, a cosmetic has been defined by the Committee as "a preparation which is applied to the skin or its appendages in order to alter its appearance, to protect it, to beautify or to promote attractiveness."

*Variation from Standard Formulas.*—If a submitted preparation consists of a standard formula (from which minor or insignificant deviations would be permitted) it is unnecessary for the manufacturer to submit data which could be obtained only at considerable expense when it would do nothing except support facts already well known in literature or elsewhere. On the other hand, when new ingredients are included about which there is insufficient information, or when formulas vary in such a way that an entirely new response may occur, it is necessary for the manufacturer or the submitting distributor to supply adequate information to prove the usefulness and safety of the preparation and to defend the claims made for it.

*Compliance with Laws.*—A declaration by the Committee that submitted formulas and advertising are acceptable merely means that compliance with the Committee's rules has occurred and does not indicate that the copy has been reviewed from the legal standpoint to determine whether it conforms with state and federal laws, this being the responsibility of the interested manufacturer or distributor.

*Terms and References Not Recognized.*—The Committee will not recognize the use of such terms as "nonallergic," "tissue cream," "hair tonic," "scalp tonic" and "cure." Nor will it recognize a reference to ailments or symptoms of disease, appeals to fear or any other technic whereby the purchaser is misled into accrediting unusual properties or significance to cosmetic products because of stated or implied misrepresentation in advertising material.

The Committee will not recognize disparaging references to competing products. Nor will it recognize references to doctors and hospitals, unless such reference is based on work consisting of controlled scientific data and is offered with full knowledge and consent of all interested parties.

*Use of Seal of Acceptance.*—Articles that are accepted by the Committee will be eligible for advertising with the Committee seal as long as the claims offered for the products remain acceptable to the Committee.

The Committee seal may not be used for a line of products unless all the products in that line are accepted, nor for a house or organization; the seal must be reserved for products.

The seal or reference to the Committee on Cosmetics should not be used in any way that detracts from their dignity.

*Advertising.*—Since all advertising for accepted products must conform to the claims recognized by the Committee on Cosmetics, advertising should be forwarded to the office of the Secretary of the Committee, American Medical Association, for review prior to release. Submission of such copy in manuscript form frequently will prevent waste of expensive type or plates when conflicts with recognized claims are discovered.

## Council on Physical Medicine and Rehabilitation

### REPORT OF THE COUNCIL

*The Council on Physical Medicine and Rehabilitation has authorized publication of the following report.*

HOWARD A. CARTER, *Secretary.*

### COLLINS VITALOMETER ACCEPTABLE

Manufacturer: Warren E. Collins, Inc., 555 Huntington Avenue, Boston 15.

The Collins Vitalometer is a spirometer designed for the determination of vital capacity and related respiratory measurements. It consists of the conventional metal cylinder or bell suspended over water in a slightly larger coaxial cylinder, and properly counterpoised. Readings are made on a dial directly connected with the chain and pulley of the counterpoise system. The height of the bell is 41 cm. (16 inches) and its diameter is 18 cm. (7 inches); its capacity is therefore of the order of 10 liters. The over-all height of the apparatus with the pulley arm telescoped is 61 cm. (24 inches), and with the pulley arm extended it is 86 cm. (34 inches). The apparatus weighs 4.5 Kg. (10 pounds); its shipping weight is 8.2 Kg. (18 pounds). Disposable mouth piece tips are available.

Collins Vitalometer

A specimen of the instrument was given a practical trial in connection with a study of spirometry in tuberculosis. No mechanical imperfections were found and the instrument was declared sturdy, practical and accurate within the limits of experimental observation.

The Council on Physical Medicine and Rehabilitation voted to include the Collins Vitalometer in its list of accepted devices.

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SATURDAY, MAY 28, 1949

## "PREVENTABLE" ACCIDENTAL AND OTHER DEATHS

Among the many unsupported claims made by the Federal Security Administrator in his promotion of a compulsory health insurance program is the reduction of the number of accidental deaths annually in this country from 100,000 to 60,000, or by 40 per cent. Above the artist's sketch opposite page one of his report to the President ("The Nation's Health—a Ten Year Program") he states: "Goal: Keep them Living—we have the knowledge to prevent 325,000 deaths each year." Thus the Administrator claims that the number of deaths each year can be reduced from the present 1.4 million to 1.1 million, which would be less than the number of deaths in the United States in any year in the twentieth century.

Obviously this reduction cannot be accomplished in an increasing and aging population because the total number dying each year in any nation depends on the number of people, their ages and the death rate per thousand at each age; nor can the annual number of deaths be kept from actually increasing during the coming years. Twenty years ago the number of deaths was one hundred thousand less than last year and life expectancy at birth was seven years less. Twenty years from now the number of deaths in our aging population may well be 1.5 to 1.6 million, the length of life will doubtlessly be greater and the mortality rate for each age will be lower than now. Health progress and the number of deaths each successive year are simply two different ideas. The task of the medical profession over the years is to raise the average age at death, reduce the importance of the "younger" causes of death and increase the importance of the "older" causes of death. Persons who do not die from the younger causes will die later from the older causes. A consideration of the "preventable" 40,000 accidental deaths in this total of "325,000 deaths each year" must not, however, obscure the impossibility of a return to the annual number of deaths which prevailed before 1900.

If the Administrator's estimate of "preventable" accidental deaths is intended as a plea for more and better safety and accident prevention measures, every one will commend the Administrator for bringing an important matter to the attention of the public. Bulletin 64, "What Is the Leading Cause of Death? Two New Measures," by the Bureau of Medical Economic Research of the American Medical Association, has shown that accidental deaths cut off more working years from the lifetimes of the American people than any one natural cause of death. "Fatal accidents" is the number one destroyer of the working years of life. The National Safety Council, the millions of plant safety workers, the traffic policemen and even the school children on patrol duty would doubtless welcome the aid and help of the vast Federal Security Agency in the prevention of accidents. Physicians realize that a comprehensive scheme for an extensive reorganization of the nation's medical services could not eliminate 40 per cent, or 40,000, of the annual 100,000 accidental deaths.

If the accidental death reports published yearly by the Kansas State Board of Health are to be taken as representative of the country as a whole, the proposal is untenable. For 1945, 1946 and 1947, a total of 4,103 fatal accidents occurred in Kansas. Of these, 1,930 deaths, or 47 per cent, occurred instantaneously and 2,468 deaths, or 60 per cent, occurred instantaneously or within one day after the fatal accident.[1] By a strange coincidence the Administrator believes that he can save 40 per cent of lives lost in all fatal accidents. According to the Kansas statistics—the best in the United States on this point—the Administrator apparently proposes to guarantee survival to all who remain alive for twenty-four hours after an accident—or to an equivalent number. The physicians would like to know how compulsory health insurance would save those lives.

## CANCERS DUE TO INDUSTRIAL TAR AND ARSENIC

In a recent editorial [1] on the excessive incidence of cancer of the lung among workers of American chromate plants, attention was called to the increasing significance of industrially important and widely used substances in the causation of cancer in man. Several reports of English investigators discuss the occurrence of cancer of the skin and lung in workers handling inorganic arsenicals [2] and of cancer of the skin in

1. Nationwide data are available for motor vehicle traffic accident fatalities only for 1945; 59 per cent died within twenty-four hours (Annual Summary of Motor-Vehicle Accident Fatalities, 1945, Vital Statistics—Special Reports, National Office of Vital Statistics, United States Public Health Service, Federal Security Agency, 1947, vol. 27, no. 6).

1. Cancer of the Lung in Chromate Workers, editorial, J. A. M. A. **138**: 823 (Nov. 13) 1948.

2. Hill, A. B., and Faning, E. L.: Studies in the Incidence of Cancer in a Factory Handling Inorganic Compounds of Arsenic, Brit. J. Indus. Med. **5**: 1-2, 1948; I. Mortality Experience in the Factory, ibid. **5**: 2-6, 1948. Perry, K.; Bowler, R. G.; Buckell, H. M.; Druett, H. A., and Schilling, R. S. F.: Studies in the Incidence of Cancer in a Factory Handling Inorganic Compounds of Arsenic: II. Clinical and Environmental Investigations, ibid. **5**: 6-15, 1948.

workers employed in gas and tar factories.[3] The English experience in regard to occupational arsenic and tar cancers is of special interest. Available data provide ample proof as to the carcinogenic properties of tar and arsenic of American manufacture.

An analysis of the cancer mortality, corrected for age and period, among workers of an English factory making arsenical sheep dip showed a notable proportional excess of deaths due to cancer over a period of thirty-five years, as compared with the cancer incidence among farmers, general laborers and artisans and shopowners of the same vicinity. This high factory incidence of cancer among arsenic workers was found to be due solely to a high incidence of cancer of the skin and lung affecting in this occupational group mainly those members engaged in the chemical processes of arsenical manufacture and exposed to the inhalation of and skin contact with arsenical dust. Although the group studied was too small to permit firm conclusions, these epidemiologic observations are in agreement with numerous casuistic reports from various countries. Since there are on record in this country only some 20 cases of cancer due to occupational exposure to arsenic, it seems pertinent to note that in the United States during 1945 the total consumption of white arsenic from domestic and foreign sources amounted to about 38,000,000 short tons. The bulk of the arsenic was used in the production of insecticides (lead arsenate, calcium arsenate, paris green) and of wood preservatives (Wolman salts containing 25 per cent sodium arsenate, zinc metaarsenite). Smaller quantities were employed in the manufacture of medicinal preparations, glass, lead base alloys, dyestuffs and chemical warfare gases and in the Thylox purification of industrial gases. Arsenic contained in and deposited on the countryside from the waste fumes of copper smelters and the slag heaps of these operations as well as arsenical insecticides accumulated over a period of years in the soil of orchards and cotton fields have created a potential environmental arsenic hazard not only to the industrially and agriculturally employed population but for the people in general living in such regions. Fruits and vegetables grown in these areas and handled in intrastate and interstate commerce, moreover, carry the hazard to even larger parts of the general population. Since cancers due to arsenic usually have a rather long latent period the etiologic connection between an occupational or environmental exposure to arsenicals and the development of cancer of the skin, lung or other mucous membranes many years later may easily be overlooked.[4]

A similar situation seems to exist in the United States in regard to the recognition and reporting of cancers due to industrial exposure to tar and pitch. There are only some 75 occupational cancers of this causation on record and not a single case of cancer caused by occupational exposure to creosote and anthracene oils. The proper significance of these figures is obtained when they are seen in the light of the following facts: The total production of gas house and coke oven tar, the most carcinogenic types of tar, stood in 1945 at 696,307,000 gallons, that of creosote oil at 27,000,000 gallons, that of tar acid oil at 13,800,000 gallons, that

## THE TRUE PHYSICIAN[1]

**By Joseph Auslander**

**Who is the true physician? He**
**Who feels a sense of ministry;**
**Who knows our ills are intertwined**
**With tentacles of heart and mind;**
**Who knows that man is truly whole**
**Only when body rhymes with soul;**
**That the world's sickness will not cease**
**Till man is with himself at peace.**

**Who is the true physician? He**
**Who from despair and fear sets free**
**Vexed spirit and tormented flesh**
**Struggling together in the mesh**
**Of human passions. Undismayed,**
**He takes the challenge on him laid,**
**And from facts cruel and uncouth**
**Creates the cold pure terms of truth.**

**Physician, you it is to whom**
**Man's body is a treacherous room**
**Where day and night and breath by breath**
**You face infirmity and death,**
**Confront the furies that by stealth**
**Slip past the sentinels of health,**
**And, with no quarter asked or given,**
**Strive as your gallant dead have striven**
**To win new ground, and to obtain**
**Some desperate reprieve from pain,**
**To fight the valiant fight until**
**Your faith, your sacrifice, your skill**
**At first confound, at last confirm**
**Man's conquest of the Conqueror Worm.**

**This, true physician, is your story,**
**Stripped of the accidents of glory,**
**Beyond all title, all esteem,**
**Servant of a tremendous dream:**
**To give man back his right to be**
**The master of his destiny,**
**To rescue from the mortal clod**
**The bright immortal son of God.**

1. Poem written for and read at the meeting of the Association of the Alumni of the College of Physicians and Surgeons of the Columbia University in Chicago, June 23, 1948.

3. Jenkins, W. D.: Dermatoses Among Gas and Tar Workers, Bristol, John Wright & Sons, Ltd., 1948, p. 54. Ross, P.: Skin Lesions Due to Pitch and Tar, Brit. M. J. **2**: 369-373, 1948.

4. Hueper, W. C.: Environmental and Occupational Cancer, Pub. Health Rep., 1948, supp. 29, p. 69.

of light tar oils at 29,000,000 gallons and that of pitch at 556,000 tons.[5]

Of the English investigators cited, Jenkins found during a ten year period among 234 tar workers 8 epitheliomas and 13 papillomas, among 96 smokeless fuel workers 3 epitheliomas and 13 papillomas, and among 3,006 gas workers 11 epitheliomas and 60 papillomas. Ross, analyzing the incidence of skin cancer among 160 tar and pitch workers during a twelve year period, observed a total of 16 epitheliomas and 102 papillomas. In 87 members of this group the employment period exceeded twelve years. Citing data collected by the Chief Inspector of Factories, Ross noted that there were recorded in England 42 cases of cancer due to tar and pitch in 1922, 97 such cancers in 1930, 119 in 1940, 111 in 1943, 160 in 1944, 176 in 1945 and 201 in 1946.

Since isolated cases of cancer have been reported in American workers engaged in a great number of different industries producing or handling tar, pitch or arsenicals, it appears appropriate that the medical profession pay increased attention to industrial and environmental sources of human cancerigenesis and prepare by prompt and complete reporting of cases of this causation a sound basis for the future control of these preventable types of cancer.

## HAZARDS OF BERYLLIUM

Public apprehension concerning the health hazards of fluorescent lights has brought another statement of facts from the Medical Advisory Committee on Beryllium.[1]

The committee reiterates its assertion that there is no danger whatever from the lights when they are intact. The possible dangers come in the destruction of old lights. Recently there have been reports of children who cut themselves on broken lights; the cuts healed slowly, and swelling was frequent. Such cuts do not cause general sickness or spread throughout the body. Surgical care is necessary if the cut refuses to heal after a period of time.

Although precautions should be taken against breathing the dust from broken fluorescent lights, records have not been published of any person's suffering injury from breathing dust after the breakage of a lamp.

The safest way to dispose of used fluorescent lights is to break them out of doors in a waste area or in a waste container; the person who breaks them should avoid breathing the dust or vapor that arises.

Possible danger occurs also in the breaking of large numbers of fluorescent lamps, either intermittently or regularly, where hours may be occupied in the operation. Instructions in these cases follow:

(*a*) Break lamps out of doors in waste disposal area or in ventilated hood. To avoid unnecessary dust, the breakage is best done within the waste container.

(*b*) The operator should be supplied with, and required to wear, a respirator approved by the United States Bureau of Mines for toxic dusts.

(*c*) Ultimate disposal of broken lamps should be such that the public and others will not be unduly exposed to powders. In situations where it is necessary to break the lamps within buildings, it should be done in an isolated room and in a hood, so as to minimize escape of dusts. Sufficient exhaust ventilation should be supplied to the hood to provide an air intake of at least 125 linear feet per minute at all hood openings.

Broken lamps should not be placed in an incinerator, but either be thrown into water or in a dump where they are not likely to be disturbed with evolution of dust.

Significant amount of mercury vapor may be found in the air during the breaking of fluorescent lamps. When exposure is frequent or continuous, measurements should be made of the amounts of mercury vapor in the air during the operation. If high levels are found, protection should be provided for the operator.

## PROPHYLAXIS OF OPHTHALMIA NEONATORUM

Credé, in 1879, advocated prevention of ophthalmia neonatorum by cleansing the birth canal with 2 per cent phenol solution and placing 1 drop of 2 per cent silver nitrate solution into the eyes of the newborn. The drop in the incidence of ophthalmia, following the adoption of the Credé method, according to Lehrfeld,[1] was due to the attempted cleansing of the birth canal rather than to the instillation of silver nitrate into the eye. Survey of the Department of Public Health records of Philadelphia for fifteen years (1920 to 1935), showed, according to Lehrfeld, that ophthalmia neonatorum has not materially decreased despite the general application of Credé's method.

Lehrfeld found, in an analysis of the records of 28,000 births occurring in six hospitals over a period of five years, that the incidence of ophthalmia neonatorum amounted to 2.2 per cent. Sorsby and his co-workers in England found in a recent survey (1942 to 1944) that the Staphylococcus was most frequently the causative organism, the gonococcus being second in frequency. Lazar stated that in his study 35 per cent of the nongonococcic types of ophthalmia neonatorum showed no micro-organisms of any kind; he assumed

5. Matthews, A. F., and Bryson, R. L.: Arsenic in Keiser, H. D.: Minerals Yearbook 1945, Washington, D. C., Government Printing Office, 1947, p. 753. DeLarlo, J. A.; Corgan, J. A., and Otero, M. M.: Coke and Byproducts, in Keiser, H. D.: Minerals Yearbook 1945, ibid., 1947, p. 958.

1. The committee includes Dr. James G. Townsend, Chief of the Division of Industrial Hygiene of the Public Health Service, Chairman; Dr. M. G. Carmody, Clifton Products Company, Painesville, Ohio; Dr. T. L. Hazlett, Westinghouse Electric Corporation, Pittsburgh; Dr. J. M. DeNardi, Brush Beryllium Company, Cleveland; Dr. W. H. Machle, New York; Dr. A. D. Nichol, General Electric Company, Nela Park, Cleveland; Dr. A. J. Vorwald, Director, The Edward L. Trudeau Foundation and the Saranac Laboratory, Saranac Lake, N. Y.; Mr. C. R. Williams, Industrial Hygiene Field Service, Liberty Mutual Insurance Company, Boston; Dr. B. S. Wolf, U. S. Atomic Energy Commission, New York, and Dr. Harry Tebrock, Medical Director, Sylvania Electric Products, Inc., Long Island, N. Y.

1. Lehrfeld, L.: Limitations of Use of Silver Nitrate in Prevention of Ophthalmia Neonatorum, J. A. M. A. **104**: 1468-1469 (April 27) 1935.

that the inflammations were due to chemical irritants such as silver nitrate. Apparently, then, ophthalmia neonatorum is not necessarily synonymous with gonorrheal ophthalmia. McEvoy [2] examined the records of 236 patients with ophthalmia neonatorum and of 87 with gonococcic conjunctivitis who were not in the newborn age group treated at the Philadelphia General Hospital during the years 1936 to 1947. Lehrfeld interprets this report as indicating that silver nitrate had failed in 236 instances, a conclusion that does not throw light on the true percentage incidence of the condition. McEvoy's comparative study indicates that local application of penicillin into the eyes of the newborn is somewhat superior to treatment with sulfonamide compounds and is much superior to the treatment of gonococcic conjunctivitis with antiseptics of the presulfonamide period. This study does not throw light on the relative merits of the Credé method and the penicillin technic.

Franklin [3] used the crystalline salt of penicillin in a concentration of 2,500 units to 1 cc. and, after irrigating the eyes with salt solution, instilled 1 drop of the penicillin solution in each eye, repeating the procedure on the three following days. Gonococcic conjunctivitis did not appear in the group in which penicillin was used, while 1 case occurred on the fourth day in the silver nitrate group, a fact without statistical significance. Franklin concluded that for prophylaxis penicillin compared favorably with silver nitrate and that it was to be preferred because the danger of permanent injury to the eyes was eliminated. Franklin, however, did not present evidence of permanent damage following the use of silver nitrate.

Berens and Foote [4] expressed the opinion that there will always be cases of ophthalmia neonatorum regardless of the effectiveness of the prophylactic agent. At least two factors may be accountable: carelessness on the part of the attendant instilling the agent and introduction of infection some time after the agent has been instilled. Evidence of permanent damage resulting from the use of 1 or 2 per cent silver nitrate has not been produced. Solutions left standing may reach a concentration as high as 50 per cent. However, supplying 1 per cent silver nitrate in paraffin-lined beeswax ampules, as is done by most health departments, has overcome the danger to the eye from high concentration of the drug.

A subcommittee of the New York Academy of Medicine on Feb. 10, 1948, recommended "that no change be made in the Sanitary Code to require the use of penicillin for the prophylaxis of ophthalmia neonatorum until there is more experience with its use." On July 20, 1948, the Council of the American Academy of Ophthalmology and Otolaryngology and the Section of Ophthalmology of the American Medical Association approved a report of a joint committee which concluded that the incomplete state of our knowledge on this subject did not justify any change in existing legislation. In full agreement with the conclusions and recommendations of the subcommittee of the New York Academy of Medicine, the group recommended that changes not be recommended now in existing laws, although possibly some form of antibiotic prophylaxis will eventually replace the present use of silver nitrate. Much further investigation of the matter is needed before any concrete recommendations can be made. Such investigations are now in progress in established clinics, and the answers may soon be forthcoming.

2. McEvoy, J. P.: Ophthalmia Neonatorum and Gonococcal Conjunctivitis, Eye, Ear, Nose & Throat Monthly **28**: 25-29 (Jan.) 1949.
3. Franklin, H. C.: Prophylaxis Against Ophthalmia Neonatorum. Clinical Comparison of Penicillin and Silver Nitrate: Preliminary Report, J. A. M. A. **134**: 1230-1235 (Aug. 9) 1947.
4. Berens, C., and Foote, F. M.: Penicillin or Silver Nitrate as a Prophylactic Agent Against Ophthalmia Neonatorum? Am. J. Pub. Health **38**: 1680-1682 (Dec.) 1948.

## NATIONAL SCHOOL HEALTH SERVICES ACT

During the Eightieth Congress considerable effort was made by special groups to secure the enactment of legislation providing for federal aid in the development of school health programs. The legislation then under consideration contained a number of basic deficiencies that prevented the American Medical Association from giving unqualified approval, although the objective has had the endorsement and the active support of the medical profession for many years. The American Medical Association has encouraged periodic examinations of school children at appropriate times during advancement in school and has stimulated the early correction of defects disclosed by such examinations. The Association has collaborated in formulating a school health program now approved by some forty-five different organizations.

A pending bill, S. 1411, to enact a National School Health Services Act, which has passed the Senate, seems scheduled for enactment by the Congress. This bill provides for the general welfare by enabling the several states to make more adequate provision for the health of school children through the development of school health services for the prevention, diagnosis and treatment of physical and mental defects and conditions. Annually $35,000,000 would be distributed to the states that have developed plans approved by the Federal Security Administrator. The bill also authorizes such other sums as may be necessary for administrative expenses. The beneficiaries of the bill will be the children in public and nonprofit nonpublic schools between the ages of 5 and 17, inclusive—more than 29,000,000 children. A state to be eligible for the federal aid must submit a plan which if it is to be accepted or approved must provide, among other things, (1) for medical and dental examinations at periodic intervals for all school children in the state, such examinations to be made, as far as practicable, at the

schools which they attend (this requirement would seem at least to discourage examinations by family physicians) and (2) for treatment of such children for physical and mental defects and conditions disclosed by such examinations, whenever the parents of the children are unable to provide the treatment. However, a state plan may provide for the prevention and treatment of such physical and mental defects and conditions of all school children, irrespective of the financial status of the parents. Too, a state plan must set forth "the manner in which payments are to be made and examinations and treatment provided." Two amendments accepted by the Senate would provide specifically for the utilization of the family physician in providing school health services and would recognize the right of a state to exempt from the program children whose parents are unwilling, on account of religious beliefs, to have the children included in the program.

On a state level, the program will be administered by the state health agency or the state education agency, or both, the decision being left apparently to each state. On a federal level, the Federal Security Administrator is named as the administrative officer. He may delegate at least some of his functions in this respect to other units of the Federal Security Agency. Previous legislation has mentioned the Children's Bureau as the appropriate federal administrative unit, and nothing apparent in the pending bill would prevent the administrator from designating that bureau.

Recognizing that state laws in some jurisdictions may prevent the distribution of funds to provide health service to children attending nonpublic schools, the bill provides that in such cases the Administrator shall withhold from the allotment of such states an amount which bears the same ratio to such allotments as the number of children in average daily attendance at nonpublic schools within the state. With the funds withheld, he will "make provision" for services to children attending the nonpublic schools comparable to the services extended to children attending public schools.

A state plan must further provide for an advisory committee to include representatives of nongovernmental organizations or groups and of state agencies concerned with health, education, child welfare and the interests of the public at large. It must provide that the school health services utilize "and develop" the qualified health, medical, dental, hospital and other related facilities already established in the state. Furthermore, it must contemplate a cooperative arrangement with the medical, dental, health, nursing, psychiatric, educational and welfare groups and organizations, and working agreements, where necessary, with state or local public health agencies having authority under state law for the care of crippled or otherwise physically handicapped children, or for other necessary health services.

The bill does not indicate that a compulsory examination or treatment requirement is contemplated as a prerequisite to school attendance, except possibly as such a requirement obtains under state law. Proper parental consent would no doubt be obtained before any medical procedure on school children under this program is undertaken. This legislation, when enacted, will affect a large segment of our population. Physicians in the several states should interest themselves actively in the formulation of state plans and afterward in their proper and rational administration.

## Current Comment

### PROFESSIONAL PRINCIPLES AND GOVERNMENTAL CONTROL

The medical profession of the United States has been engaged now for some thirty-five years in opposing the establishment of a federal bureaucracy for the development, control and distribution of medical care. History indicates that medicine not infrequently is the first line of attack by those who favor governmental domination. Once medicine is brought under central management, other professions, industries and trades succumb. A recent issue of the periodical called *The Theatre,* distributed with programs in the theaters of New York City, considers the attempt in connection with consideration of an education bill by the present Congress to provide for the allocation of $1,000,000 for the establishment of a national theater. Although this idea has been before the theatrical profession for almost ten years, it has now been revived after an abeyance during the last war. Commenting on this subject, Mr. Eugene Burr says:

> . . . though the establishment of a national theatre would unquestionably be an excellent thing, two factors must be borne in mind in any planning. Some way (Thespis alone knows what it could be) would have to be found to guarantee that there would be no bureaucratic domination, that posts in the national theatre would not become political spoils, that the national theatre would be controlled by no exclusive group within the theatre itself. In the second place, jobs in the national theatre would have to be given on the basis of ability rather than need—and this, at least, is a fact whose importance is acknowledged in all of the current plans. A national theatre could not be the means of aiding incompetent amateurs to break into the professional stage. Participants would have to base their claims on ability, not on penury or political affiliation.
>
> But how to establish such standards of ability is a problem; for there can be no absolute standards in any art, but merely evaluations according to individual taste. If somehow someone can solve that problem, without establishing a theatrical clique as the dictator of all standards—and if someone can tell how to guarantee that a national theatre will not become bureaucratic—then a national theatre will be an altogether wonderful thing.
>
> But without those conditions it could become merely a means of disseminating party propaganda, a refuge for political henchmen, an artistic plum for a small group within the theatre itself, or a haven for needy incompetents. And having no national theatre at all is preferable to something like that.

# ORGANIZATION SECTION

## Official Notes

### MORE INTERNS PROTEST NATIONALIZED MEDICINE

The interns of Ancker Hospital, St. Paul, have addressed the following letter to the editor of *The Interne*, a magazine said to be the publication of the interns' organization, protesting unanimously their disapproval of the platform adopted by the Association of Internes and Medical Students at their convention in 1948 supporting a government-sponsored, national health insurance program. The Association of Internes and Medical Students apparently includes relatively few interns and residents, but claims to represent all:

"We, the internes of Ancker Hospital, St. Paul, Minnesota, have just recently received the February, 1949, issue of *The Interne* containing the report on the AIMS convention of 1948. We were chagrined to note the resolution, stating the AIMS platform in regards to a government-sponsored, national health insurance program, which was 'passed by the panel,' and 'greeted with enthusiasm and endorsed unanimously by the convention.'

"We, the internes of this 700 bed city and county Ancker Hospital, are unanimously opposed to any such government-sponsored program. We are fully cognizant of, and thankful for, the fact that the platform adopted by AIMS is certainly not supported by the vast majority of internes in the United States. We note with pride the advancements made by a free, democratic system of medicine and are confident that such a system will be well able to meet the medical needs of the American people.

Yours truly,
THE INTERNES OF ANCKER HOSPITAL."
[Signed by each intern of Ancker Hospital]

### NEW COMMITTEE TO REVIEW HEALTH BILLS

A newly appointed committee, headed by Dr. Harvey Stone of Baltimore, will meet in Washington, D. C., in the near future to review and study all types of health bills introduced in Congress. The committee hopes to coordinate the medical profession's views relating to all legislation.

The bills to be studied will deal with all types of federal regulations as they pertain to medical care, especially the Hill and Taft bills as they relate to public welfare and to the medical profession.

Dr. Elmer Henderson, Louisville, Chairman of the Board of Trustees, and Dr. George Lull, Secretary and General Manager, will serve as ex officio members of the committee; other members are: Drs. R. L. Sensenich, South Bend, President of the American Medical Association; Louis H. Bauer, Hempstead, New York, Chairman of the Executive Committee of the Board of Trustees; R. B. Robins, Camden, Ark.; John W. Cline, San Francisco; Frank Borzell, Philadelphia; Frank Lahey, Boston, and James R. McVay, Kansas City.

### COOPERATING WITH COOPERATIVES

The Council on Medical Service of the American Medical Association and representatives of national labor, farm and cooperative organizations representing consumers of medical care met in the Palmer House, Chicago, April 29.

The following joint statement was issued by Dr. James R. McVay of Kansas City, Mo., chairman of the Council on Medical Service, and Jerry Voorhis, executive secretary of the Cooperative Health Federation of America, representing the consumer groups:

"It is the sense of the individuals at this meeting that we are in substantial agreement that voluntary prepayment medical care plans should be developed that will assure the public of the highest quality of medical service and that full assurance be provided for the maintenance of the quality of good medical care; and that a joint committee be appointed—three by the Council on Medical Service and three by organizations of consumers of medical care—to consider the establishment of standards in conformity with the above principles; and that such committee report back to this assembly at 10 o'clock, Saturday, June 4, in Atlantic City."

## Washington Letter

*(From a Special Correspondent)*

May 23, 1949.

### National Health Legislation Witnesses Scheduled

Representatives of more than twenty national organizations will express their views on national health legislation during the first three weeks of Senate committee hearings that were scheduled to open on May 23. Majority of them will be heard during the two week period beginning May 30, since the opening days of the extended hearing were to be devoted to testimony by members of Congress and federal officials supporting the various bills under consideration. These include the Thomas-Murray-Dingell bill calling for compulsory health insurance, the Hill and Taft voluntary assistance measures and the Lodge bill, which provides for "free drugs" to the medically indigent.

The following organizations have been invited to send representatives to testify at the hearings: American Medical Association, American Hospital Association, Congress of Industrial Organizations, Blue Cross Commission, Associated Medical Care Plans, American Federation of Labor, Association of State and Territorial Health Officers, American Public Health Association, Catholic Hospital Association, American Protestant Hospital Association, Americans for Democratic Action, American Dental Association, Cooperative Health Federation of America, Association of Land Grant Colleges and Universities, American Association of Universities, Association of American Medical Colleges, American Council on Education, National Association of State Universities, Association of Schools of Public Health, Association of American Dental Schools, National Association for Practical Nursing, American Nurses Association, National Organization for Public Health Nursing and National League of Nursing Education.

### Representative Andersen: "I Pity The People of America"

Representative H. Carl Andersen (Republican, Minnesota) on May 16 delivered a speech on the House floor in which he described socialized medicine as a national calamity if the medical care available at the Capitol to members of Congress is typical of the Truman-Ewing plan. His speech was precipitated by a syndicated newspaper column (Drew Pearson) which stated that the dispensary type of services afforded to members of Congress is essentially socialized medicine.

The Minnesotan said he went to the dispensary with an injured wrist and was advised to soak it in hot epsom salts.

"Fortunately, I had occasion to go to Minnesota three weeks later and, as my wrist was still very painful, contacted my home town doctor who asked me: 'Did you have an x-ray taken of the wrist after the accident?' I answered, 'No, none was suggested.' My doctor in Tyler, Minn., then took an x-ray and found that the wrist had been broken. He said that it was extremely fortunate that the bone had knitted together properly without medical attention.

"All I have to say is that, if the medical service we have available here in the Capitol is a sample of socialized medicine, I certainly pity the people of America if that legislation is enacted into law."

### Proprietary Association to Hear Ewing and Dr. Cline

The pros and cons of compulsory health insurance and of the Taft and Hill voluntary assistance plans will be discussed at the sixty-seventh annual convention of the Proprietary Association of America at White Sulphur Springs, W. Va., June 1-3. Speakers will include Federal Security Administrator Oscar R. Ewing, on "The President's Health Program; Its Scope and Objectives"; Dr. John W. Cline, former president of California Medical Association, on "Medicine's Answer to the Truman Proposal for Socialized Medicine," and John W. McPherrin, editor of *American Druggist*, who will report on observations in England while studying its National Health Service system.

To date the Proprietary Association, whose members produce an estimated 80 per cent of the packaged medicines manufactured in the United States, has not taken an official position for or against any of the national health plans pending in Congress. Its headquarters are in Washington. F. J. Cullen, M.D., is executive vice president.

### Propagandizing by Federal Security Agency Criticized

Establishment of a Department of Welfare, which would give the present Federal Security Agency cabinet status, was strongly opposed in a House floor speech (May 17) by Representative Clare Hoffman (Republican, Michigan). Such action, he said, would mean surrender "to the bureaucrats in the executive department, in this instance to the Federal Security Agency." He charged the Federal Security Agency Administrator not only with disseminating propaganda but with attempting to justify such activity.

## Medical Legislation

### STATE LEGISLATION

#### Delaware

**Bill Vetoed.**—S. C. Res. 20, which would have memorialized the Congress of the United States to refrain from imposing on the citizens of this nation **any form of compulsory insurance** or any system of medical care designed for national bureaucratic control, was vetoed by the Governor on April 28, 1949.

#### Maine

**Bill Enacted.**—H. 2076 was approved May 5, 1949. It provides that the use of **electrolysis for the removal of hair** is not a part of the practice of hairdressing and beauty culture and is prohibited except under the direction of a licensed physician.

#### Maryland

**Bills Enacted.**—H. 152 has become chapter 704 of the Laws of 1949. It amends the law relating to the **practice of chiropractic** by, among other things, providing that a license to practice chiropractic shall not include the right to practice obstetrics. S. 16 has become chapter 669 of the Laws of 1949. It **creates an anatomy board** to have charge of the distribution of certain dead bodies which come under its control. Such bodies shall be used only for the promotion and application of the medical sciences. S. 329 has become chapter 682 of the Laws of 1949. **It amends the law relating to the practice of medicine** by providing that applicants for a license who graduated from a college in a foreign country, the entrance requirements, standard of education and requirements for graduation of which are equivalent to the standard defined by the Association of American Medical Colleges or the Intercollegiate Committee of the American Institute of Homeopathy shall be eligible to take the examination for licensure in Maryland.

#### Michigan

**Bills Enacted.**—H. Res. 24 was adopted May 9, 1949. It provides for the creation of a special committee to investigate the advisability of establishing a program of **rehabilitation for alcoholics.** S. C. Res. 19 was adopted May 6, 1949. It memorializes the Congress of the United States not to adopt legislation relative to **socialized medicine.**

#### Ohio

**Bill Enacted.**—H. 308 was approved May 12, 1949. It makes it unlawful to deliver any of the **barbiturates** except by a pharmacist on the original prescription of a person licensed in the state to prescribe and administer drugs.

#### Pennsylvania

**Bill Enacted.**—S. 665 has become Act No. 284 of the Acts of 1949. It provides that certain property to be conveyed to the University of Pittsburgh shall be used for the extension of its Medical Center which will include the **Graduate School of Public Health.**

#### Rhode Island

**Bills Enacted.**—H. 906 was approved May 12, 1949. It provides for the licensing of **maternity hospitals.** S. 35 was approved May 3, 1949. It creates a special commission to investigate the advisability of establishing facilities for the study, **treatment and care of inebriates.**

#### Vermont

**Bills Enacted.**—H. J. Res. 22 was approved April 26, 1949. It authorizes the governor to appoint a committee composed of a physician and two other persons to make a study of the approximate number of persons in the state suffering from **epilepsy** and the feasibility of a state program for the care, treatment and rehabilitation of persons so afflicted. H. 139 was approved May 4, 1949. It authorizes the governor to appoint a committee to make a study of the treatment and rehabilitation of **alcoholics.** H. 338 was approved May 5, 1949. It provides regulations for the **licensing of hospitals** in the state.

## Coming Medical Meetings

American Medical Association, Atlantic City, June 6-10. Dr. George F. Lull, 535 N. Dearborn St., Chicago 10, Secretary.

American Academy of Neurology, French Lick, Indiana, French Lick Springs Hotel, June 1-3. Dr. Joe R. Brown, 19 Millard Hall, University of Minnesota, Minneapolis 14, Secretary.

American Academy of Tuberculosis Physicians, Atlantic City, Hotel Dennis, June 4. Dr. Oscar S. Levin, P. O. Box 7011, Denver 6, Colo., Secretary.

American Association of Railway Surgeons, Chicago, Drake Hotel, June 30-July 2. Dr. Chester C. Guy, 5800 Stony Island Ave., Chicago 37, Secretary.

American College of Chest Physicians, Atlantic City, Ambassador Hotel, June 2-5. Mr. Murray Kornfield, 500 N. Dearborn St., Chicago 10, Executive Secretary.

American College of Radiology, Atlantic City, Chalfonte-Haddon Hall, June 5. Mr. William C. Stronach, 20 N. Wacker Drive, Chicago 6, Secretary.

American Dermatological Association, Hot Springs, Va., May 25-28. Dr. Louis A. Brunsting, 102 Second Ave. S.W., Rochester, Minn. Secretary.

American Gastro-Enterological Association, Atlantic City, Claridge Hotel, June 3-4. Dr. Dwight L. Wilbur, 655 Sutter Street, San Francisco 2, Secretary.

American Gastroscopic Society, Atlantic City, Claridge Hotel, June 3-4. Dr. J. Edward Berk, 255 S. 17th St., Philadelphia 3, Secretary.

American Goiter Association, Madison, Wis., Hotel Loraine, May 26-28. Dr. Thomas C. Davison, 478 Peachtree St., N.E., Atlanta 3, Ga., Secretary.

American Medical Women's Association, Atlantic City, June 4-5. Dr. Augusta Webster, 104 S. Michigan Ave., Chicago, Secretary.

American Neurological Association, Atlantic City, Chalfonte-Haddon Hall, June 13-15. Dr. H. Houston Merritt, 710 W. 168th St., New York 32, Secretary.

American Ophthalmological Society, Hot Springs, Va., The Homestead, June 2-4. Dr. Maynard C. Wheeler, 30 W. 59th St., New York, Secretary.

American Proctologic Society, Columbus, Ohio, May 31-June 4. Dr. W. Wendell Green, 1838 Parkwood Ave., Toledo 2, Ohio, Secretary.

American Radium Society, Atlantic City, June 5. Dr. Hugh F. Hare, 605 Commonwealth Ave., Boston 15, Secretary.

American Society for the Study of Sterility, Atlantic City, Hotel Strand, June 5. Dr. Walter W. Williams, 20 Magnolia Terrace, Springfield 8, Mass., Secretary.

American Therapeutic Society, Atlantic City, June 2-5. Dr. Oscar B. Hunter, 915 Nineteenth St. N.W., Washington, D. C., Secretary.

Association for the Study of Internal Secretions, Atlantic City, June 3-4. Dr. Henry H. Turner, 1200 N. Walker St., Oklahoma City 3, Secretary.

Idaho State Medical Association, Sun Valley, June 20-23. Dr. Alfred M. Popma, 220 N. First St., Boise, Secretary.

International Congress on Rheumatic Diseases, New York, Hotel Waldorf-Astoria, May 30-June 3. Dr. Philip S. Hench, Mayo Clinic, Rochester, Minn., Chairman, American Committee.

Maine Medical Association, Poland Spring, Poland Spring House, June 19-21. Dr. Frederick R. Carter, 142 High St., Portland 3, Secretary.

New Hampshire Medical Society, Newcastle, Hotel Wentworth, June 14-15. Dr. Carleton R. Metcalf, 5 S. State St., Concord, Secretary.

Society for Investigative Dermatology, Atlantic City, Ritz Carlton Hotel, June 11-12. Dr. S. William Becker, 55 E. Washington St., Chicago 2, Secretary.

Society of Biological Psychiatry, Atlantic City, Chalfonte-Haddon Hall, June 12. Dr. George N. Thompson, 1136 W. Sixth St., Los Angeles, Secretary.

Western Branch of American Public Health Associaiton, Los Angeles, Hotel Biltmore, May 30-June 1. Mr. Walter S. Mangold, University of California, Berkeley, Calif., Secretary.

# GOVERNMENT SERVICES

## ARMY

### USE OF WACS IN HOSPITALS

While Wacs are already being used in a variety of assignments in Army hospitals, a special effort is to be made to measure the maximum extent to which they can serve in hospital positions traditionally filled by men. The experiment, scheduled to start June 1, will run for one and a half to two years, and they will work both at Murphy General Hospital and at the Lovell Section at nearby Fort Devens.

This experiment will be a guide to determine to what extent enlisted women could be used in hospitals in the event of a national emergency and a consequent man power shortage. They will operate the hospital pharmacy, and will work as photographers, x-ray technicians, mess attendants and stewards, supply clerks and physical reconditioning instructors. Wacs already are filling most of these positions throughout the Army Medical Department, but this is the first time that all such jobs in one hospital will have been filled by enlisted women. A special board of officers, consisting of representatives of the Surgeon General's Office, Women's Army Corps and the hospital staff, will follow the progress of the experiment.

### PHYSICAL MEDICINE

A conference on Physical Medicine in Army Hospitals was held April 25-29 in the Surgeon General's Office to review the regulations and policies regarding physical medicine and to propose new regulations in the light of the experiences of two years of physical medicine as a separate service in the Army. Participants included Dr. Frank H. Krusen, director of physical medicine, Mayo Clinic, Rochester, Minn.; Dr. Donald L. Rose, director of physical medicine, University Medical Center, Kansas City, Kan.; Col. Emmett M. Smith, chief, physical medicine service, Walter Reed Hospital; Col. Harold B. Luscombe, M.C., chief, physical medicine service, Fitzsimmons Hospital, Denver; Col. Arthur E. White, M.C., chief, physical medicine service, Letterman Hospital, San Francisco, and Capt. E. J. Lorenze, M.C., acting chief, physical medicine consultants division, Surgeon General's Office.

### OFFICERS SELECTED FOR ADVANCED TRAINING

The following medical officers have been selected for advanced training in the civilian schools and hospitals indicated:

| Officer | Institution | Subject |
|---|---|---|
| Raymond E. Duke, Col. | University of Minnesota, Minneapolis | Public Health |
| Benjamin H. Sullivan Jr., Lieut. Col. | American College of Physicians, Philadelphia | Cardiovascular disease |
| Arthur E. H. Knox, First Lieut. | St. Luke's Hospital, New York | Medicine |
| Walter F. Reeves, First Lieut. | Indiana University Medical Center, Indianapolis | Intern training |
| Lester I. Nienhuis, First Lieut. | University Hospital, Ann Arbor, Mich. | Residency in general surgery |
| George W. Pogson, First Lieut. | Kansas City General Hospital, Kansas City, Mo. | Residency in internal medicine |
| Franklin M. Lockwood, First Lieut. | Kansas City General Hospital, Kansas City, Mo. | Residency in surgery |
| Irvin L. Schweitzer, First Lieut. | Mercy Hospital, Chicago | Residency in medicine |
| Harry J. Umlauf Jr., First Lieut. | Children's Hospital Society, Los Angeles | Residency in pediatrics |
| Arthur J. Moseley, First Lieut. | Grady Memorial Hospital, Atlanta, Ga. | Residency in medicine |
| Max W. Pegram, First Lieut. | Hospital of St. Barnabas, Newark, N. J. | Residency in plastic surgery |
| Kent T. Woodward, First Lieut. | Georgetown University Hospital, Washington, D. C. | Residency in medicine |
| Dean F. Winn Jr., First Lieut. | San Francisco Hospital, San Francisco, Calif. | Residency in surgery |
| William W. Tucker, First Lieut. | St. Luke's Hospital, San Francisco, Calif. | Residency in surgery |
| William W. Thompson, First Lieut. | Duke Hospital, Durham, N. C. | Residency in pediatrics |
| Edwin E. Pontius, First Lieut. | Indiana University Medical Center, Indianapolis | Residency in clinical pathology and pathology |
| Joseph A. Roy, First Lieut. | De Paul Hospital, St. Louis | Residency in surgery |
| Hugo M. Cardullo, First Lieut. | Bellevue Hospital, New York | Residency in pediatrics |

## AIR FORCE

### ARCTIC AEROMEDICAL LABORATORY

The Air Force Arctic Aeromedical Laboratory has completed its second winter of operations at Fairbanks, Alaska. The laboratory is attempting to collect physiologic, biochemical and psychologic data on the difficulties of living in the Arctic. Preliminary biochemical investigations conducted at the Arctic Laboratory demonstrated that blood coagulation times are prolonged under Arctic conditions, and current studies are aimed at determining the stage of the clotting process that is involved. Animal studies are in progress to determine the reasons for the greater tolerance of some species for Arctic cold than others.

Colonel Jack Bollerud, head of the Laboratory, states that living under conditions of Arctic weather and isolation carries with it a serious morale problem. Men sent to Ladd Field accordingly are being given standard psychologic tests on arrival and monthly for one year in an attempt to fathom the factors involved. It is expected that personality responses and changes thus determined will aid in the development of psychologic selection technics for Arctic duty.

During the relatively mild Alaskan summer, the base line psychologic program is continued, but most of the cold weather research is suspended. Newly arrived personnel are being trained for their role in the active winter program for the year ahead.

### INITIATE GENERAL PRACTICE BRANCH

Major General Malcolm C. Grow, the Air Surgeon, announces the initiation of a general practice branch in the Air Surgeon's office, to be charged with the development of training opportunities and careers for general practitioners serving at Air Force installations. According to current Air Force organization, about 70 per cent of physicians serving with Air Force units are general practitioners. Of the remainder, 5 per cent are staff and administrative personnel and 25 per cent are specialists. General Grow characterized the general practitioner as "the backbone of the Air Force medical service." Under the new program the general practitioner will be enabled to enter into a proposed residency program to be operated in the general hospital setup. The residency program will offer the general practitioner access to latest technical developments in medical and surgical specialties. Emphasis will be placed on internal medicine, surgical practices, pediatrics and obstetrics. The new general practice branch will work cooperatively with the Surgeon General's career program for medical officers.

# VETERANS ADMINISTRATION

## ELIMINATE THIRTEEN BRANCH OFFICES

The Veterans Administrator announces the selection of five key points from which medical supervision of hospitals and other medical matters will be carried on. They are Atlanta, Boston, Fort Snelling, Minn., San Francisco and St. Louis. The plan for medical supervision from these points resulted from the elimination of the thirteen branch offices of the Veterans Administration where medical activities previously were under the direction of branch medical directors. All functions of former branch office medical staffs are now centered in the office of the Chief Medical Director in Washington. The Administrator said, "In connection with medical matters handled in Washington, it is necessary that we have representatives traveling throughout the country. For the sake of reduced travel expense and other economies, certain Central Office representatives will be stationed at strategic points, to serve as the eyes and ears of the Chief Medical Director." He emphasized that "in no sense will these official stations become operating offices. They will simply be points from which Central Office personnel will travel. This change will bring supervision of the Chief Medical Director closer to hospital and other medical activities in the field, thereby assuring maintenance of the finest medical service to veterans."

## RESIDENCIES IN NEUROLOGY

Several openings are available in the residency training program in neurology at the Veterans Administration Hospital, Coatesville, Pa. The program, organized by the Philadelphia Deans Committee, has been approved by the American Medical Association. This residency covers a period of three years or less, depending on the previous experience of an applicant, and is designed to prepare residents for certification in neurology by the American Board of Psychiatry and Neurology. The program includes rotation through the Veterans Administration Hospital, Coatesville, Pa., Veterans Administration Regional Office, Philadelphia, and the Philadelphia General Hospital. Applications should be sent to the Manager, Veterans Administration Hospital, Coatesville, Pa.

## "THE BEST IN MEDICINE"

The Veterans Administration opened an exhibit for two weeks beginning May 2 in the Union Station Concourse, Washington, D. C., demonstrating that the Veterans Administration medical program offers veterans "The Best in Medicine."

# PUBLIC HEALTH SERVICE

## DR. APPLEWHITE TO RETIRE

Dr. Calvin C. Applewhite, who entered the United States Public Health Service in 1915, will retire from the service October 1. He is known in many states especially for helping to build and strengthen local health services. A graduate of Vanderbilt University Medical School, he has for the last eight years been a Regional and District Medical Director for the Public Health Service.

## CANCER RESEARCH GRANTS

The Public Health Service announced April 28 additional grants amounting to $293,452 to support laboratory and clinical research and $79,853 for research facilities. These grants are in addition to research grants of $671,200 announced on March 25. The grants for research facilities were $30,385 to Meharry Medical College, Nashville, Tenn., and $49,468 to the Institute for Cancer Research in Philadelphia. Among other grants announced is $30,000 for work at Children's Hospital, Boston, under the direction of Dr. Sidney Farber to attempt to discover more effective chemotherapeutic treatment of leukemia; another grant was $12,560 to the State University of Florida for work under the direction of Dr. Francis E. Ray, who will study the experimental production of gastric cancer in animals by chemical means. These grants were recommended by the National Advisory Council at its meeting in March.

## NEW MEMBERS OF MENTAL HEALTH COUNCIL

The Surgeon General announces the appointment, effective July 1, of two new members of the National Advisory Mental Health Council. They are Dr. Franz Alexander, director, Chicago Institute for Psychoanalysis, and Dr. S. Bernard Wortis, chairman, Department of Psychiatry, New York University Medical College, replacing Dr. William C. Menninger and Dr. John Romano, whose three year terms on the Council expire. Dr. Alexander received his medical training in Budapest and was director of the Berlin Institute for Psychoanalysis before coming to the United States in 1930. Dr. Wortis, a graduate of Cornell University Medical School, taught at his alma mater and at Johns Hopkins University before going to New York University Medical College in 1942.

# MISCELLANEOUS

## ACCIDENT RATE IN COAL MINES

The number of American coal miners killed and injured in the nation's coal mines in 1948 in relation to the total man-hours of exposure was lower than in any year except 1944 and 1945, Bureau of Mines Director James Boyd announces. In 1948 the combined fatal and nonfatal injury rate for each million man-hours of exposure to hazards during work was 63.46, the Director said. This was slightly lower than the corresponding rate of 63.62 for 1947 and the rate of 65.35 for 1946. During 1944, when production was at a high level, the combined fatal and nonfatal injury rate per million man-hours was 60.26—lowest on record. A total of 64, 989 nonfatal and fatal injuries occurred in 1944 during 1,078,474,377 man-hours of work. In 1948, miners worked 867,500,000 man-hours with a total of 55,055 injuries, 1,010 fatal and 54,045 nonfatal.

On a tonnage basis, the fatal and nonfatal injury rate for 1948 was the best annual record in the statistical history of the nation's coal mining industry. This rate, according to recently revised data, was 84.56 per million tons of coal produced. Part of the improvement shown by the figures calculated on a tonnage basis is due to higher productivity resulting from increased mechanization and strip mining.

The number of deaths occurring in Pennsylvania anthracite mines in 1948 was estimated at 140, according to recently revised figures, and the fatality rate per million man-hours at 0.92—the best on record. In bituminous coal mines, 870 men lost their lives, and the fatality rate per million man-hours was 1.22. The combined 1948 death rate for both anthracite and bituminous coal mines was placed at 1.16 per million man-hours.

Accident figures for 1948 recently revised by the Bureau also placed the number of nonfatal injuries in anthracite mines at 12,330, and in bituminous coal mines at 41,715. A total of 55,055 men were killed and injured, a 7.3 per cent drop from the number of deaths and injuries in 1947.

In 1948, six major disasters—single accidents in which 5 or more men were killed—resulted in 49 deaths in bituminous coal mines. No major disasters occurred in anthracite mines.

Injury and employment statistics are based on monthly reports received by the Bureau of Mines from bituminous coal and anthracite mines producing about 75 per cent of the coal mined in the United States. All figures are subject to revision.

# Medical News

**(Physicians will confer a favor by sending for this department items of news of general interest: such as relate to society activities, new hospitals, education and public health. Programs should be received at least two weeks before the date of meeting.)**

## CALIFORNIA

**Report of Eye Bank.**—The Stanford University Eye Bank supplied corneas for twenty-four eye graft operations during its second year of operation. Hospitals in San Francisco were the major source of corneas, but eyes were also supplied from Oakland, San Jose, Auburn, Burlingame, Redwood City, Stockton, Tulare and San Diego. Many of the operations performed at Stanford Hospital were on patients from out of town. All Pacific Coast eye surgeons qualified to perform the eye graft operation are eligible to use the services of the Eye Bank, which operates without cost to either patient or surgeon except for a small service fee. Persons who wish to will their eyes to the Eye Bank for use in corneal transplant operations after their deaths may do so through forms available on application to the Eye Bank, Stanford University Hospitals, Clay and Webster Streets, San Francisco.

## COLORADO

**Harvard Alumni Lecture.**—Dr. Marius N. Smith-Petersen, Newton, Mass., gave the second Harvard Lecture at the University of Colorado Medical Center, Denver, May 19. This lectureship is sponsored by the alumni of the Harvard Medical School in the Rocky Mountain region.

**Course in Regional Anesthesiology.**—An intensive one week postgraduate course in regional anesthesiology will be held at the University of Colorado Medical Center, Denver, June 27 to July 1. The subject will be presented by cadaver dissections, lectures, clinical demonstrations and supervised practice in the various technics covered in the course. The guest lecturer will be Dr. Emery A. Rovenstine, New York University–Bellevue Medical Center. Admission is open to all physicians who are members of their constituent medical societies or the American Medical Association. The registration fee is $5 and tuition will be $45. Inquiries should be made to the Director of Graduate and Postgraduate Medical Education, University of Colorado Medical Center, Denver.

## CONNECTICUT

**Cancer Award to Dr. Smith.**—The American Cancer Society on May 4 gave the 1949 Connecticut Cancer Award for distinguished service in cancer control to Dr. George M. Smith of Pine Orchard. The award follows fifty years of service. He has been a member of the Board of Scientific Advisers of the Jane Coffin Childs Fund, medical director of the Anna Fuller Fund and executive director of the National Advisory Cancer Council. In recent years he has helped to guide the cancer work initiated by the National Research Council. Dr. Smith received his medical degree from Columbia University College of Physicians and Surgeons, New York, in 1905. Last year he was named emeritus professor by Yale, which had granted him the LL.D. degree in 1947 largely in recognition of his contributions to the cancer problem.

## FLORIDA

**Graduate Course in Cardiovascular Diseases.**—The Department of Medicine of the Graduate School of the University of Florida announces a special course on cardiovascular diseases, which will be presented June 14-17 at the George Washington Hotel in Jacksonville. The recognition and management of heart conditions of particular interest to physicians in general practice will be featured. Dr. R. Bruce Logue of Emory University School of Medicine, Atlanta, will present the lectures.

## ILLINOIS

**Camp for Diabetic Children.**—A summer camp for diabetic children of the Chicago area is being opened this summer from August 18 to September 1 at Bartlett. The counselors and facilities of Sunset Camp, which is run in conjunction with the James Herrick House for children with crippled hearts, will give diabetic children summer camp experience. The Chicago Diabetes Association will furnish nurses, dieticians and resident physicians trained in the care of diabetic children. Girls from 7 to 16 and boys from 7 to 9 inclusive will be accepted. Charges are reasonable and may be scaled down if necessary. Application blanks are available to physicians from Mrs. Robert Pennock, chairman, Summer Camp Committee, Chicago Diabetes Association, 1931 Lincoln Park West, Chicago; telephone Yards 7-5600, Ext. 234.

### Chicago

**Dedicate Cancer Exhibit.**—The new cancer exhibit at the Museum of Science and Industry was dedicated April 28. Charles F. Kettering, Dayton, Ohio, was the principal speaker. The exhibit, covering 3,200 square feet and financed by the Illinois Division of the American Cancer Society, explains the problems cancer presents and is expected to help speed cancer control. The exhibit was designed and produced under supervision of Professor Thomas S. Jones and Miss Ruth Coleman of the medical illustration department of the University of Illinois. It was opened to the public May 6.

**Appoint Superintendent of Tuberculosis Sanitarium.**—Dr. Otto L. Bettag, Pontiac, has been appointed medical superintendent and tuberculosis control officer of the City of Chicago Municipal Tuberculosis Sanitarium. The appointment combines two offices formerly held by Dr. George C. Turner, who was medical superintendent, and Dr. Arthur W. Newitt, who resigned several months ago as tuberculosis control officer. Dr. Bettag, medical director and tuberculosis control officer of Livingston County, has been in charge of the tuberculosis section of the Illinois Department of Public Safety for ten years. He has also been thoracic surgeon at the Veterans Administration Hospital, Hines.

**Dr. Richard H. Young Named Dean at Northwestern.**—Dr. Richard H. Young has been appointed dean of Northwestern University Medical School to succeed Dr. J. Roscoe Miller, who becomes president of the University in July. Dr. Young, now dean of the College of Medicine of the University of Utah, Salt Lake City, is a native Chicagoan, who received his doctor of medicine degree from Northwestern in 1930. After serving an internship and residency at St. Luke's Hospital, Chicago, he did graduate study, principally in hematology, at the University of Oregon Medical School, Portland, and the University College Medical School of the University of London, England. Dr. Young was a member of Northwestern's department of medicine from 1931 to 1945, serving as head of the experimental medicine division the last seven years of that period. In 1945 he became director of the student health service of the university. He was awarded the bronze star for meritorious achievement as a member of the 12th General Hospital staff in the recent war, in which he served as a lieutenant colonel and chief of medicine.

**Lay Cornerstone for Cancer Research Hospital.**—The cornerstone for the seven story Nathan Goldblatt Memorial Hospital at the University of Chicago was laid May 17. The $2,500,000 cancer research hospital was established in 1946 with a gift of $1,000,000 to the university by the Goldblatt Brothers Foundation in memory of Nathan Goldblatt, who died of cancer in 1944. Dr. Leonard Scheele, Surgeon General, U. S. Public Health Service, spoke at the luncheon for the foundation trustees, the women's board and the Nathan Goldblatt Society for Cancer Research, and delivered the principal address at the cornerstone ceremony. Other speakers included President Ernest C. Colwell, Dr. Lowell T. Coggeshall, dean of the division of biological sciences, Maurice Goldblatt, Gov. Adlai Stevenson and Mayor Martin H. Kennelly. This, it is said, will be the first university hospital in the country with the entire staff engaged full time in cancer research and treatment. A second cancer hospital, the Argonne Cancer Research Hospital to be built by the United States Atomic Energy Commission adjacent to the Goldblatt hospital, will also be devoted to full time research treatment of cancer patients with radioactive isotopes.

The Goldblatt Brothers Foundation is a charitable trust established in 1936 by the Goldblatt family to administer their contributions for activities in the fields of social service and medical research.

## IOWA

**A Course in Clinical Audiometry.**—An intensive two week course in clinical audiometry will be offered at the State University of Iowa, Iowa City, June 14-28. The course will include, among other things, lectures on audiometry, lip reading, speech training for the hard of hearing, psychologic problems of the acoustically handicapped and clinical otolaryngology; laboratory work; hearing aid fittings, and demonstrations by John C. Steinberg, Ph.D., of the Bell Telephone Laboratories and Mrs. Bernice Rutherford of the Rehabilitation Center, St. Paul, Minn. For information address: Professor Wendell Johnson, Director, Speech Clinic, State University of Iowa, Iowa City.

## MASSACHUSETTS

**Dr. Clark to Head Massachusetts General Hospital.**—Dr. Dean A. Clark, associate professor of public health practice at Columbia University, has been appointed head of Massachusetts General Hospital, Boston, to succeed Dr. Nathaniel W. Faxon, who has reached the retirement age. Dr. Clark, a graduate of Johns Hopkins University School of Medicine, Baltimore, 1932, was a National Research Council fellow in neurophysiology at Cornell University Medical College; house physician at Phipps Psychiatric Clinic, at Johns Hopkins University in Baltimore, and an intern at Trudeau Sanatorium, Trudeau, N. Y. He was the first chief medical officer of the Federal Office of Vocational Rehabilitation and was on loan to the American Red Cross in 1944-1945 with the rank of surgeon in the regular corps in the U. S. Public Health Service. Since 1945 he has been on leave of absence from the service as medical director of the Health Insurance Plan of Greater New York. He will assume active direction of the hospital as soon as he is relieved of his present responsibilities in New York.

## MISSISSIPPI

**State Medical Meeting.**—The Mississippi State Medical Association held its annual meeting in Biloxi May 10-12, under the presidency of R. B. Caldwell, Baldwin. Out of state speakers included:

Frank T. Mitchell, Memphis, Experience of a Pediatric Consultant in Public Health.
Theodore A. Watters, New Orleans, Common Psychiatric Problems and Psychosomatic Disorders in General Practice.
W. Banks Anderson, Durham, N. C., Congenital and Traumatic Vascular Lesions of the Eye and Adnexia—Kodachrome Clinic.
Lyle M. Sellers, Dallas, Texas, The Frontal Sinus—A Problem in Diagnosis and Treatment.
Jack S. Guyton, Baltimore, Surgery of Horizontal Strabismus.
Arthur J. Walker, New Orleans, Chills and Fever Versus Malaria.
Guy H. Williams and Eric Bell, Cleveland, Present Day Status of Multiple Sclerosis.
Maxwell E. Lapham, New Orleans, Suggested Program for Better Distribution of Medical Service to the Public.
Theo. H. Hanser, St. Louis, Hidden Genito-Urinary Conditions Parading as Abdominal Conditions.

The Ewing Fox Howard oration honoring Dan J. Williams was delivered by Henry Boswell of Sanatorium. The Woman's Auxiliary to the association met May 9-11.

## MISSOURI

**Personal.**—Dr. Robert E. Schlueter, honorary librarian of the St. Louis Medical Society, was given the annual award by the society at a recent dinner meeting. The speakers on the occasion were Dr. Robert E. Kane of St. Louis and Chauncey D. Leake, Ph.D., Galveston, Texas.

**Dedicate Headquarters to the Late Dr. O'Reilly.**—The recently opened headquarters and clinic of the St. Louis Society for Crippled Children has been dedicated to the late Dr. James A. O'Reilly, who founded the St. Louis society and was for twenty years its president. The one story building is designed to suit specific functions. Front and rear entrances are on ground level; doors are wide enough to permit easy passage of wheel chair patients, and a hallway 35 feet long serves as an exercise corridor. There is also a large playground for the children.

## NEW YORK

**Graduate Education.**—The Medical Society of the State of New York with the cooperation of the New York State Department of Health has arranged the following graduate lectures: Ontario County Medical Society, meeting at the Country Club, Geneva, June 14 at 8 p. m., will hear Dr. G. Gowing Broad, Syracuse, speak on "Diagnosis in Disease of the Anorectum." The Chenango County Medical Society will hear Dr. Charles L. Steinberg, Rochester, speak on "Chronic Arthritis: Its Diagnosis and Management" at its meeting in the Oxford Inn, Oxford, June 14 at 12 noon.

**State Sets Up Graduate Scholarships.**—For the first time in its history New York has established state scholarships for professional education in medicine and dentistry. The new law fixes the maximum as one hundred and leaves the monetary value and duration to the Board of Regents and the state budget director. The establishment of these graduate scholarships is an outgrowth of studies made by the Temporary Commission on the Need for a State University, which found that economic harriers constituted a substantial handicap for many persons desiring to enter these professions. The law also authorizes the regents with the approval of the budget director to increase the number of undergraduate awards. Formerly these were set at five for each of the one hundred fifty assembly districts of the state. Undergraduate scholarships have carried an annual stipend of $350 for a four year period.

## New York City

**Residencies Available.**—The Psychiatric Division of the Kings County Hospital, Brooklyn, is expanding its residency training program and has positions available particularly for residents requiring only one more year and seeking third year training. The positions pay $1,560 with maintenance. Inquiries should be addressed to Dr. Sam Parker, Director of Psychiatry, 606 Winthrop Street, Brooklyn 3.

**Personal.**—Edward H. L. Corwin, Ph.D., executive secretary of the Committee on Public Health Relations of the New York Academy of Medicine since its founding in 1911, has been appointed associate professor of public health practice in the Columbia University School of Public Health, a part time appointment; Dr. Corwin continues with the academy. ——Dr. Benjamin Jablons has been appointed visiting physician (peripheral vascular diseases) at Goldwater Memorial Hospital.

**Dr. Bassler Honored.**—On the occasion of his fiftieth anniversary in the practice of medicine Dr. Anthony Bassler was guest of honor at a testimonial dinner at the Hotel Commodore, May 1. The speakers included Dr. William Morrison, president of the National Gastroenterological Association; Dr. Martin E. Rehfuss, professor of medicine at Jefferson Medical College of Philadelphia; Msgr. John Curry, head of the Catholic hospitals of New York City, and Rev. Walsh, professor of psychology at Fordham University; Dr. Foster Kennedy, professor of neurology at Cornell University Medical College; Dr. Elihu Katz of the New York Polyclinic; Hon. Ferdinand Pecora and Hon. Peter Schmuck, Judges of the Supreme Court. Dr. Bassler was presented with a book of letters and a gold medal. He is the author of textbooks on gastroenterology.

## NORTH CAROLINA

**Faculty Appointments.**—George O. Doak, Ph.D., chemist of the U. S. Public Health Service, has been appointed associate professor of experimental medicine at the University of North Carolina School of Public Health, Chapel Hill, effective July 1. Dr. Doak has his M.A. and Ph.D. degrees from the University of Wisconsin, Madison. Prior to becoming associated with the Public Health Service he was instructor in medicine and a research associate in bacteriology at Johns Hopkins School of Hygiene and Public Health, Baltimore.

Dr. Frederick A. Thompson Jr. will join the staff of the school of public health July 1 as assistant professor of experimental medicine. He has been assigned by the U. S. Public Health Service as chief of the biology section of the laboratory of experimental medicine. He received his M.D. degree from Duke University School of Medicine, Durham, and at the time of his appointment was serving his residency at Duke Hospital.

## OHIO

**Fellowships in Industrial Medicine.**—The University of Cincinnati is the recipient of a new fellowship in industrial medicine at the Institute of Industrial Health of the University's Graduate School of Arts and Sciences. It was established by the Texaco Company, New York. Two similar fellowships have been granted by the Ethyl Corporation and by the university itself.

**Rural Medical Scholarships.**—The Ohio State Medical Association has approved a rural medical scholarship plan "to stimulate interest on the part of rural young men and women in the study of medicine, with the belief that because of their interest in rural life, they will later establish medical practice in rural communities." The scholarships will be administered by the Committee on Rural Health, with the aid of an advisory committee composed of representatives from the various rural and educational organizations. Each grant will be $500 per school year, awarded for a four year period, subject to acceptable work on the part of the student. No obligations other than that will be attached to the scholarship. It is restricted to Ohio residents but may be used at any approved medical school in the country.

## RHODE ISLAND

**Tom Spies Given Chapin Award.**—Dr. Tom D. Spies, professor of nutrition and metabolism and chairman of the department of Northwestern University Medical School, Chicago, received the annual Charles V. Chapin Memorial Award, presented May 11 at the annual dinner meeting of the Rhode Island Medical Society in Providence. The award was established in 1942 by the medical society in honor of the late Dr. Chapin, a native of Providence and one of the foremost public health workers. Dennis J. Roberts, mayor of Providence, presented the award, with a medal provided by a standing

committee of the City Council. Dr. Spies, who is also director of the nutrition clinic at Jefferson-Hillman Hospital, Birmingham, Ala., delivered the Chapin Lecture on "Recent Advances in Nutrition."

## TEXAS

**Personal.**—Dr. Carl A. Moyer, professor of experimental surgery at Southwestern Medical College, Dallas, was the 1949 recipient of the Dallas Southern Clinical Society's Marchman Award for research into the fluid balance of the human body.

**Gift for X-Ray Equipment.**—The Sealy and Smith Foundation of Galveston has given $22,000 to the John Sealy Hospital of the University of Texas Medical Branch, Galveston, for x-ray equipment in the Special Surgical Unit under the direction of Dr. Truman G. Blocker Jr., Galveston. The Special Surgical Unit, accommodating fifty-six beds, is devoted to plastic and maxillofacial surgery and neurosurgery.

**Nobel Prize Winner Lectures.**—The annual lectureship sponsored by Alpha Omega Alpha, honorary medical fraternity, at the University of Texas Medical Branch, Galveston, was given this year by Arne Tiselius, Ph.D., professor of biochemistry at the University of Uppsala, Sweden, and Nobelate for 1948. Professor Tiselius discussed the application of chromatographic methods to clinical problems. At the annual initiation and banquet of Alpha Omega Alpha, Professor Tiselius described the development of dextrane as a plasma substitute.

## VERMONT

**Course in Cardiovascular Disease.**—The Cardiovascular Unit, recently established on a cooperative basis by the College of Medicine of the University of Vermont, Burlington, and the Bishop DeGoesbriand Hospital in Burlington, will conduct a refresher course on cardiovascular disease June 13-18. Guest speakers will be Dr. Paul D. White, Harvard Medical School, Boston, and a consultant of the National Heart Institute, and Dr. Mercier Fauteux, McGill University, Montreal, Canada. In addition 12 members of the University of Vermont medical faculty will take part in the program.

**Study of Tendon Transplantation.**—The National Foundation for Infantile Paralysis announces a one year grant to the division of orthopedic surgery of the University of Vermont College of Medicine, Burlington, for a study of the results of tendon transplantation, particularly in the lower extremities. The work will be carried out by Dr. Raymond Kuhlman, fellow in orthopedic surgery, under the direction of Dr. John F. Bell, associate professor in that division. The follow-up service of the Crippled Children's Division of the Department of Health will cooperate in the study.

## WEST VIRGINIA

**Personal.**—Dr. Delivan A. MacGregor, of Wheeling, has been appointed by Dr. Thomas G. Reed, Charleston, president of the West Virginia State Medical Association, as a member of the advisory committee to the United Mine Workers Welfare and Retirement Fund. He will represent the Northern Panhandle. Dr. Ray M. Bobbitt, of Huntington, is chairman of the committee and the other members are Drs. Fred Richmond, of Beckley, and John P. Helmick, of Fairmont.

**Licenses Revoked.**—The licenses of the following doctors to practice medicine in West Virginia have been revoked: Wilkin R. Stevens, of Welch, license no. 6473, dated July 10, 1941, and Lawrence T. Browning, license no. 5394, dated Dec. 14, 1927. The orders entered by the public health council assigned as the reason for the revocation in each of these cases the doctor's conviction of a felony charge.

**State Health Conference.**—The annual State Health Conference, combining sessions of the State Health Officers' Conference and the West Virginia Public Health Association, will be held June 2-3 at the Daniel Boone Hotel, Charleston. At the general session Dr. Newman H. Dyer, state health commissioner, Charleston, will speak on "Public Health Forecast"; Dr. John D. Porterfield, director of health, Columbus, Ohio, on "Local Health Problems," and Dr. Russell C. Bond, Wheeling, on "The West Virginia Pediatric Study." Guest speaker at the banquet Thursday evening will be Dr. James G. Townsend of the U. S. Public Health Service, Washington, D. C., whose subject will be "Atmospheric Pollution." A panel discussion on "Integrating Services to Serve the Public" will be held Friday after section meetings. At 7:30 p. m. Friday Roy E. Dickerson, executive secretary of the Cincinnati Social Hygiene Society, will discuss "What Is Family Life Education?"

## HAWAII

**Territorial Medical Election.**—At the annual meeting of the Hawaii Territorial Medical Association May 7 in Honolulu, Dr. Howard E. Crawford, Hilo, became president and Dr. Rogers Lee Hill, Honolulu, was chosen president elect. Drs. Irvin L. Tilden and Edwin K. Chung-Hoon, both of Honolulu, were elected secretary and treasurer respectively for three year terms.

**Enlarge Blood Bank.**—The Blood Bank of Hawaii, Honolulu, is to be enlarged by a 16 by 80 foot extension to the building to meet increasing demand for blood and blood products. The growing volume of service reflects expanded and improved procedures for processing and using blood rather than a rise in the number of donors, according to Dr. Forrest J. Pinkerton, director. The blood bank is now giving transfusions in its own offices to persons referred there by physicians, a practice that results in a saving to patients of time and money. The bank services twenty-eight hospitals on four islands, and the average civilian patient load has gone up from about 300 per month in wartime to nearly 1,000. During the war blood was simply turned over to the military, who prepared their own equipment for administering it. For most civilian hospitals, however, the blood bank prepares the administration sets. Rh typing, done only sporadically during the war, is now a routine process at the blood bank.

Another process developed at the bank since the war is the titration of all type O bloods. The blood bank is a nonprofit organization operating for the benefit of the community. It charges patients $7.50 for service and requests replacement of blood by a donor, setting $42.50 as the charge for the blood, to discourage patients from buying it outright. In 1948 the bank accepted blood of 10,186 persons. Over 90 per cent of the demand is for whole blood. When unused blood becomes outdated, it is processed into plasma. Dr. Pinkerton has recently completed arrangements with Irwin Memorial Blood Bank of San Francisco and the Blood Bank Commission of the California State Medical Association for mutual assistance in the event of war or a community disaster of catastrophic proportions. A similar agreement with the bank in Seattle is now under consideration.

## GENERAL

**University of Pennsylvania Class Reunion.**—The 1939 class of the University of Pennsylvania School of Medicine, Philadelphia, will hold a reunion and supper in the Solarium of the Claridge Hotel, Atlantic City, N. J., June 5, from 5 to 7 p. m.

**Hahnemann Medical Alumni Reunion.**—An alumni reunion of the Hahnemann Medical College will be held June 8 at 6 p. m. in the Chalfonte Music Room, Chalfonte-Haddon Hall, Atlantic City, N. J. Tickets may be purchased in advance from the college alumni office.

**Tuberculosis Physicians Meeting.**—The American Academy of Tuberculosis Physicians will hold its annual meeting June 4 at the Hotel Dennis, Atlantic City, N. J., under the presidency of Dr. Robert A. Peers, Colfax, Calif. Presentation of awards will take place at the luncheon at 12:30 p. m.

**$250,000 for Research on Heart Disease.**—Research grants totaling $250,000 have been allocated by the American Heart Association to 26 investigators and 6 medical schools and hospitals for studies in heart and circulatory diseases. Award selections were made from among 121 requests totaling $1,400,000. Dr. Tinsley R. Harrison, Dallas, president of the American Heart Association, stated that "All the requests were of high caliber and deserving of fulfilment."

**Librarian Honored.**—Mrs. Eileen R. Cunningham, librarian of the Vanderbilt University School of Medicine, Nashville, Tenn., has been chosen the first recipient of the Medical Library Association's Marcia C. Noyes Award in recognition of her achievements in medical librarianship. Mrs. Cunningham is the author of "Classification for Medical Literature," now in its third edition. She has held offices in numerous library associations and has served on many of their committees.

**Electroencephalographic Society Meeting.**—The American Electroencephalographic Society will hold its annual meeting at the Chalfonte-Haddon Hall, Atlantic City, N. J., June 11-13, under the presidency of Dr. Frederick A. Gibbs, Chicago. The program includes a symposium on corticothalamic pathways to be held Sunday morning under the chairmanship of Dr. A. Earl Walker, Baltimore. The symposium is being held in collaboration with the American Branch of the International League Against Epilepsy.

**Meeting on Medical Missions.**—All physicians and medical students are cordially invited to attend a public meeting on overseas mission medical work at 8 p. m. June 5, in the Central Methodist Church, 1213 Pacific Avenue, Atlantic City, N. J. Several outstanding medical missionaries will give accounts of their work abroad. A motion picture on medical mission work in the Congo will be shown. The meeting is sponsored by the Christian Medical Council for Overseas Work.

**Awards for Rehabilitation Work.**—The National Council for Rehabilitation, at a meeting at the Astor Hotel, New York, April 21, conferred 1949 awards on Lionel Barrymore, Thomas E. Millsop, president of the Weirton Steel Company and Dr. Royd R. Sayers, medical director of the United Mine Workers of America, for their activities in behalf of the disabled. Dr. Henry H. Kessler, Newark, N. J., was reelected head of the council.

**Meeting of Physical Therapy Association.**—The American Physical Therapy Association will hold its annual conference at the Copley Plaza Hotel, Boston, June 19-24. Among the subjects to be presented are "Rehabilitation of the Hemiplegia Patient," "Neurological Aspects of Cerebral Palsy," "Poliomyelitis," "Multiple Sclerosis," "Some Research Problems in Physical Therapy," "Some Psychiatric Problems Related to Arthritis" and "Fractures." On Friday afternoon various physical therapy clinics in the Boston area will hold "open house."

**Research Fellowships in Medicine.**—The American College of Physicians announces that a limited number of fellowships in medicine will be available from July 1, 1950 to June 30, 1951. These fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in internal medicine. The stipend will be from $2,200 to $3,000. Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, and must be submitted in duplicate not later than Oct. 1, 1949.

**Award Abel Prize in Pharmacology.**—At the Detroit meeting of the American Society for Pharmacology and Experimental Therapeutics, Mark Nickerson, Ph.D., assistant professor of pharmacology, University of Utah, College of Medicine, Salt Lake City, was awarded the 1949 John J. Abel Prize in Pharmacology for his research on "Pharmacology of the B-Haloalkylamines: a New Class of Adrenergic Blocking Agents." This prize of $1,000 and a bronze medal has been donated to the society by the Eli Lilly Co., Indianapolis. The 1950 prize will be awarded at the Atlantic City meeting of the society to be held the week of April 9, 1950. Information concerning this award can be obtained from the secretary of the society, Dr. Harvey B. Haag, Medical College of Virginia, Richmond 19, Va.

**World Medical Association Publishes Bulletin.**—The first issue of the *World Medical Association Bulletin*, a quarterly, appeared in April under the editorship of Dr. Morris Fishbein, Chicago, and nine collaborating editors representing several other nations. The same articles appear in English, French and Spanish in corresponding columns of its 32 pages. The bulletin is not to be a medical journal; "Its purpose is wholly in the field of medicine as related to social advancement, to government, to war, and to the standards of medical care." The World Medical Association was established in Geneva in 1947 to raise the standards of medical education throughout the world and, correlated with this, the delivery of the highest quality of medical service. The $10 World Medical Association annual fellowship dues, which should be sent to the association's address, 2 East 103rd Street, New York 29, includes subscription to the bulletin.

**Recommendations on Maternal and Child Health.**—A series of proposals were formulated by the World Health Organization's Expert Committee on Maternal and Child Health, which met in Geneva in January. These are to serve as the basis for discussion and action at the second World Health Assembly in Rome in June. Among the recommendations were the following: establishment of a special Health Education Service within the World Health Organization; stimulation of research and provision of information to governments in the form of monographs and bibliographies; sending of expert advisers and demonstration teams to countries requesting them; expansion of the existing fellowship program and stimulation of training of nurses, midwives; close cooperation with UNICEF in mass immunization campaigns and development of child guidance clinics, and with UNICEF and FAO in stimulating production and distribution of safe milk.

**Vascular Surgeons' Meeting.**—The Society for Vascular Surgery is holding its annual session June 5 at the Hotel Dennis in Atlantic City, N. J. All physicians are welcome to attend. The program is as follows:

George D. Lilly and Robert M. Lee, Miami, Fla., Complications of Anti-Coagulant Therapy.
Julian Johnson, Philadelphia, Experimental and Clinical Use of Vein Grafts to Replace Large Arteries.
Michael Radakovich and W. J. Merle Scott, Rochester, N. Y., Venous and Lymphatic Stasis in the Lower Extremities.
Richard Warren, Boston, Venous Pressures in the Lower Extremities as a Pre-Operative Study to Determine a Method of Treatment for Varicose Veins.
Thomas L. Stokes and John H. Gibbon Jr., Philadelphia, Observations on the Temporary Artificial Maintenance of the Circulation.
Emile Holman, San Francisco, President's Address: Problems in the Dynamics of Blood Flow.
Davitt A. Felder, Fiorindo A. Simeone and Robert R. Linton, Boston, Evaluation of Sympathetic Neurectomy in Raynaud's Disease.
Helen B. Taussig, Baltimore, Diagnosis and Differential Diagnosis of Cyanotic Malformations Amenable to Surgery.
Kenneth N. Campbell, Detroit; Bradley M. Harris, Ypsilanti, Mich., and Frederick A. Coller, Ann Arbor, Mich., Follow-Up Study of Patients with Thrombo-Angiitis Obliterans.
Lewis H. Bosher Jr. and Isaac A. Bigger, Richmond, Va., Study of Collateral Circulation Following Excision of Arteriovenous Fistulas.
Harris B. Shumacker Jr., Indianapolis, Study of Factors Influencing Effect of Arterio-Venous Fistulas on Size of the Heart.
Irving Leinwand, J. William Hinton and Jere W. Lord Jr., New York, Hypertensive Vascular Disease with Quadrilateral Raynaud's Syndrome Treated by Total Sympathectomy.

Dinner will be at 7 p. m.

**Special Society Elections.**—The American Association of Pathologists and Bacteriologists at its recent meeting in Boston elected Drs. Shields Warren, Alan R. Moritz and Sidney Farber, all of Boston, president, secretary and treasurer, respectively.——At the annual meeting of the Association of Schools of Public Health in Ann Arbor, Mich., last year's officers were reelected. They are: Brigadier General James S. Simmons, Boston, president, and Dr. Gaylord Anderson, Minneapolis, secretary-treasurer.——The Southeastern Section of the American Urological Association at its recent annual meeting installed Dr. James J. Ravenel, Charleston, S. C., as president and chose Drs. Edgar Burns, New Orleans, president elect and Russell B. Carson, Fort Lauderdale, Fla., secretary-treasurer.——At the fourth annual meeting of the Council of the New England State Medical Societies held recently in Boston, Dr. Norman A. Welch, physician in chief at Carney Hospital, Boston, was elected president and Dr. Roland E. McSweeney, Brattleboro, Vt., president of the Vermont State Medical Society, vice president. John E. Farrell, Sc.D., executive secretary of the Rhode Island Medical Society, was reelected secretary-treasurer.—— The American Academy of Orthopaedic Surgeons at its meeting in Chicago in January installed Dr. Mather Cleveland, New York, as president, and chose Dr. Guy Caldwell of Tulane University of Louisiana School of Medicine, New Orleans, as president elect. Dr. H. Relton McCarroll is treasurer and Dr. Harold B. Boyd, Memphis, Tenn., secretary.——The American Society of Pharmacology and Experimental Therapeutics at its Detroit meeting April 18-22 elected Drs. Carl F. Schmidt, Narberth, Pa., as president, Harvey B. Haag, Richmond, secretary, and Ko Kuei Chen, Indianapolis, treasurer.——The American Society for Clinical Investigation at its meeting in Atlantic City May 2 chose T. Hale Ham, Brookline, Mass., as president.

## Marriages

Charles W. Hoffman Jr., Baltimore, to Miss Tove Poulsen of Perth Amboy, N. J., in Fort Dix, N. J., April 30.

Waldron Raymon Gardiner Jr., to Miss Jacqueline Sabina Heims, both of San Francisco, April 30.

Harold Jack Tausend, Houston, Texas, to Miss Mary Louise Nesbit of Madison, Wis., April 23.

Malachi Wilson Sloan II, Detroit, to Miss Jane Mayne Taylor of Allentown, Pa., April 23.

Samuel Earl Upchurch to Miss Alia Ann Samford, both of Birmingham, Ala., April 20.

Homer Curtiss Merrick Jr., to Miss Margaret Anne Paul, both of Norfolk, Va., April 10.

Hugh McIntyre Caldwell to Miss Vivian Laura Moll, both of Columbus, Wis., April 28.

Robert R. Gillespy Jr. to Miss Sena Rae Matthews, both of Birmingham, Ala., April 26.

Robert Bragg Hagood, Lowndesboro, Ala., to Miss Georgia Bell of Fayetteville, April 9.

# Deaths

**Eugene Hillhouse Pool** ✠ Locust Valley, N. Y.; born in New York June 3, 1874; Columbia University College of Physicians and Surgeons, New York, 1899; emeritus professor of clinical surgery at the Cornell University Medical College in New York; joined the faculty of his alma mater as assistant demonstrator of anatomy in 1901; rose through the ranks until, in 1915, he was named professor of clinical surgery, holding that post until 1938; in 1948 retired as a life trustee of Columbia University, a position he had held since 1939, after having served as an alumni representative; a member of the consulting board of cancer research at Columbia; secretary of the Section on Surgery of the American Medical Association from 1916 to 1919 and chairman in 1922 and 1923; past president of the New York Academy of Medicine, American College of Surgeons and the American Surgical Association; member of the International Surgical Association, Southern Surgical Association and the Society of Clinical Surgery; fellow of the American College of Surgeons; member of the founders group of the American Board of Surgery; decorated for distinguished service with the medical corps of the American Expeditionary Forces in France, at which time he served as a lieutenant colonel and directed surgical work in the St. Mihiel and Meuse-Argonne offensives; served as surgeon on the advisory board of the New York City committee of the American Society for the Control of Cancer; as a representative of the New York Academy of Medicine, appointed by Governor Lehman in 1933 as chairman of a committee that studied medical abuses in connection with the administration of the Workmen's Compensation Law; in 1934 was named administrative consultant in surgery for all the city hospitals in New York; formerly on the joint administrative board of the Columbia-Presbyterian Medical Center; served as senior attending surgeon of the New York Hospital and surgeon in chief emeritus of the Hospital for the Ruptured and Crippled; consulting surgeon, Presbyterian, French, Harlem and Woman's hospitals, New York Infirmary for Women and Children, the North Country Community Hospital in Glen Cove, the Elizabeth A. Horton Memorial Hospital in Middletown, N. Y., the Monmouth Memorial Hospital in Long Branch, N. J., the United Hospital in Port Chester, N. Y., the New York Eye and Ear Infirmary and Central Islip (N. Y.) State Hospital; died April 9, aged 74.

**Robert Moseley Yergason** ✠ Hartford, Conn.; born in Hartford Oct. 3, 1885; Columbia University College of Physicians and Surgeons, New York, 1909; specialist certified by the American Board of Orthopaedic Surgery; member of the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; served during World War I; visiting orthopedic surgeon, St. Francis and Mount Sinai hospitals in Hartford, and Home for Crippled Children, Newington; consulting orthopedic surgeon, Veterans Administration Hospital in Newington, Manchester Memorial Hospital in Manchester, Windham Community Memorial Hospital in Willimantic, Meriden Hospital in Meriden, Day Kimball Hospital in Putnam, William W. Backus Hospital in Norwich, Litchfield County Hospital in Winsted and Neuro-Psychiatric Institute of the Hartford Retreat; awarded the Silver Beaver by the Boy Scouts of America; died in St. Francis Hospital March 24, aged 63, of pneumonia.

**Irving Hotchkiss Pardee** ✠ New York; born in New York Jan. 26, 1892; Columbia University College of Physicians and Surgeons, New York, 1915; professor of neurology and executive officer of the department of neurology at his alma mater; member of the Association for the Study of Internal Secretions; member and formerly vice president of the Association for Research in Nervous and Mental Disease and the American Neurological Association; past president of the New York Neurological Society; served with the American Expeditionary Forces during World War I; affiliated with the Hospital for Special Surgery, New York Neurological Institute and St. Luke's Hospital in New York, Yonkers (N. Y.) General Hospital, Tuxedo Memorial Hospital, Tuxedo Park, and the North Country Community Hospital in Glen Cove; died in the New York Hospital April 10, aged 57.

**Joe R. Clemmons** ✠ New York; born in Longview, Texas, Sept. 4, 1896; University of Tennessee College of Medicine, Memphis, 1924; member of the American College of Hospital Administrators, American Public Health Association and the American Hospital Association; for many years director of the Associated Hospital Service; served in France during World War I; cited by President Truman for his work as chairman of the New York State Procurement and Assignment Service for Physicians, which recruited doctors for the armed forces in World War II; formerly assistant director of Strong Memorial Hospital in Rochester, N. Y., and medical superintendent of the Macon (Ga.) Hospital; for many years medical director and executive vice president of Roosevelt Hospital, where he died April 2, aged 52.

**David Hastings Atwater** ✠ Rochester, N. Y.; Syracuse University College of Medicine, 1902; for many years county coroner; served during World War I; died in Strong Memorial Hospital February 7, aged 73, of cerebral hemorrhage.

**Paul Eve Bain,** Pawnee, Ill.; Barnes Medical College, St. Louis, 1899; died March 7, aged 70, of coronary occlusion and prostatitis.

**Henry Lester Baker** ✠ Chicago; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1898; an Associate Fellow of the American Medical Association; died March 5, aged 79, of coronary heart disease.

**George Tilman Banker** ✠ Elizabeth, N. J.; Cornell University Medical College, New York, 1911; in 1946 received a certificate of appreciation from the War Department for three or more years on the Induction Examining Board in Newark; member of the board of education; on the staff of Elizabeth General Hospital; died in Plainfield March 6, aged 66, of heart disease.

**James Nelson Barger,** Albany, Mo.; University Medical College of Kansas City, Mo., 1898; died in St. Francis Hospital, Maryville, March 1, aged 75, of multiple sclerosis.

**Andrew Peter Barnai,** Chicago; Regia Universitá degli Studi di Bologna. Facoltá di Medicina e Chirurgia, Italy, 1937; member of the American Medical Association; served during World War II; affiliated with the Chicago State Hospital; died April 17, aged 35.

**George Calvin Berkheimer,** Windber, Pa.; College of Physicians and Surgeons, Baltimore, 1905; member of the American Medical Association; past president of the Somerset County Medical Society; died in Philipsburg March 4, aged 77, of cerebral hemorrhage.

**Bo Carr Bowell,** La Porte, Ind.; College of Physicians and Surgeons of Chicago, 1895; formerly county coroner; on the staff of Holy Family Hospital and Fairview Hospital, where he died March 2, aged 79, of cerebral hemorrhage.

**Pierre Brunelle,** Lowell, Mass.; McGill University Faculty of Medicine, Montreal, Canada, 1896; member of the American Medical Association; served as chairman of the city board of health; died February 11, aged 76, of cerebral hemorrhage.

**Joseph Aaron Carter,** Seattle; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1898; served during World War I; died in the Veterans Administration Hospital March 8, aged 82, of cerebral hemorrhage.

**James Burnett Clark,** Springfield, Mo.; Kansas Medical College, Medical Department of Washburn College, Topeka, 1909; died in Kansas City, March 1, aged 78, of uremia.

**Arthur Hiram Congdon** ✠ Schenectady, N. Y.; Albany (N. Y.) Medical College, 1915; on the staff of Ellis Hospital; died in Richmond, Va., March 4, aged 58, of coronary occlusion.

**George Lindsay Cook** ✠ Tampa, Fla.; University College of Medicine, Richmond, 1913; specialist certified by the American Board of Pediatrics, Inc.; member of the American Academy of Pediatrics; fellow of the American College of Physicians; on the staffs of Tampa Municipal and St. Joseph's hospitals; died March 8, aged 62, of heart disease.

**Ninian J. Cooper,** Kramer, Pa.; College of Physicians and Surgeons, Baltimore, 1894; died March 7, aged 83, of arteriosclerosis.

**Baron Francis Cornett,** Bluefield, W. Va.; Atlanta College of Physicians and Surgeons, 1902; died in St. Luke's Hospital, February 18, aged 76, of carcinoma of the rectosigmoid.

**Louis Ward Croke** ✠ Boston; Tufts College Medical School, Boston, 1911; formerly faculty member of the Massachusetts Institute for Technology; affiliated with the Liberty Mutual Insurance Company; died February 15, aged 63, of cardiac decompensation, amputation of right leg in April 1947, and embolism.

**Donald Ray Davis** ✠ Dodge City, Kan.; University of Southern California School of Medicine, Los Angeles, 1939; served overseas during World War II; died in Wichita, March 4, aged 36, of uremia and streptococcic septicemia.

**Albert Simeon Dolloff** ✙ Goshen, Conn.; Dartmouth Medical School, Hanover, N. H., 1891; an Associate Fellow of the American Medical Association; member of the New Hampshire Medical Society; died in Torrington, March 6, aged 86, of cardiorenal vascular disease.

**Harry Edward Dorwart** ✙ Lexington, Neb.; Creighton University School of Medicine, Omaha, 1927; died recently, aged 45, of coronary disease.

**Sim Driver** ✙ Dallas, Texas; Baylor University College of Medicine, 1920; clinical associate professor of orthopedic surgery at the Southwestern Medical College; member of the Clinical Orthopaedic Society and the American Academy of Orthopaedic Surgeons; fellow of the American College of Surgeons; served during World War I; on the staffs of the Baylor University, St. Paul's, Methodist, Medical Arts and Parkland hospitals; died in the Gaston Hospital February 27, aged 58, of mesenteric thrombosis.

**Maurice Samuel Duchin,** Cambridge, Mass.; Chicago Medical School, 1930; died in Peter Bent Brigham Hospital, Boston, February 5, aged 46.

**James Henry Gasson,** Shenandoah, Iowa; John A. Creighton Medical College, Omaha, 1898; member of the American Medical Association; died in the Iowa Methodist Hospital, Des Moines, March 5, aged 79, of myocardial infarction and coronary sclerosis.

**Louis Herbert Gaus,** Albany, N. Y.; Albany Medical College, 1907; served during World War I; consulting oculist to the Moses-Ludington Hospital, Ticonderoga; medical adviser for Selective Service during World War II; died in St. Peter's Hospital, March 6, aged 64, of coronary occlusion.

**Joseph Enoch Gichner,** Baltimore; University of Maryland School of Medicine, Baltimore, 1890; member of the American Medical Association; professor of clinical medicine and physical therapy emeritus at his alma mater; died March 8, aged 85, of gangrene of the left foot and generalized arteriosclerosis.

**Joseph Goethe Graver,** Cleveland; College of Physicians and Surgeons, Baltimore, 1907; member of the American Medical Association; on the staffs of the University Hospitals; died in Cleveland Clinic Hospital February 9, aged 68, of coronary occlusion.

**Frank Joseph Guenther,** La Grange, Texas; Medical Department of Tulane University of Louisiana, New Orleans, 1909; member of the American Medical Association; past president of the Fayette County Medical Society; county health officer; affiliated with La Grange Hospital; died March 4, aged 63, of heart disease.

**Darwin Walton Hall** ✙ Kansas City, Mo.; University Medical College of Kansas City, 1896; an Associate Fellow of the American Medical Association; died March 3, aged 75, of coronary thrombosis.

**Aldace Walker Hammond** ✙ Beaver Dam, Wis.; Rush Medical College, Chicago, 1920; for many years health officer; on the staffs of Lutheran Deaconess and St. Joseph's hospitals; died March 10, aged 56, of coronary thrombosis.

**Louis Everett Hanisch** ✙ Omaha; University of Nebraska College of Medicine, Omaha, 1916; instructor in surgery at his alma mater; fellow of the American College of Surgeons; served in France during World War I; affiliated with the Lutheran Hospital; died March 13, aged 59, of coronary occlusion.

**Clarence Edwin Harco** ✙ Newcomerstown, Ohio; Hahnemann Medical College and Hospital of Philadelphia, 1945; served during World War II; died in February, aged 29.

**Isaac Carrington Harrison,** Danville, Va.; University of Virginia Department of Medicine, Charlottesville, 1895; member of the American Medical Association; past president of the Medical Society of Virginia; served on the state board of medical examiners, as chairman of the school board and as a member of the police commission; on the staffs of Hilltop Sanatorium and Memorial Hospital; died in Westbrook Sanatorium, Richmond, March 12, aged 78, of pneumonia following fracture of a hip as the result of a fall.

**John George Henson,** Huntley, Ill.; Chicago College of Medicine and Surgery, 1908; served during World War I; on the staffs of Sherman Hospital and St. Joseph Hospital in Elgin; died February 27, aged 65, of coronary embolism.

**Harry Campbell Hill** ✙ Streator, Ill.; Rush Medical College, Chicago, 1894; an Associate Fellow of the American Medical Association; died March 9, aged 79, of coronary occlusion.

**Alwin Joseph Holden,** Chicago; Bennett Medical College, Chicago, 1915; served during World War II; died in American Hospital February 25, aged 54, of bronchopneumonia.

**Foster Miller Hull,** El Monte, Calif.; College of Physicians and Surgeons, Los Angeles, 1912; died February 8, aged 60.

**Donald Henry Jessop** ✙ Portland, Ore.; University of Oregon Medical School, Portland, 1909; fellow of the American College of Surgeons; on the staff of St. Vincent's Hospital; formerly chief surgeon of the Union Pacific Railroad Company; died March 9, aged 73, of cerebral accident and Parkinson's disease.

**Lewis Karnopp** ✙ Wautoma, Wis.; College of Physicians and Surgeons of Chicago, 1894; served during World War I; local surgeon for the Chicago and Northwestern Railroad for many years; died March 5, aged 78, in a motor car accident.

**Ronald Bradshaw Kieffer** ✙ Toledo, Ohio; Ohio State University College of Medicine, Columbus, 1937; formerly practiced in Napoleon, Ohio, where he was county coroner; served on the staff of the William W. Roche Memorial Tuberculosis Hospital; died March 1, aged 39, of tuberculosis.

**Secord Herbert Large,** Cleveland; Trinity Medical College, Toronto, Canada, 1893; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology, of which he had been treasurer and comptroller, American Laryngological Association and American Laryngological, Rhinological and Otological Society; on the staff of St. Vincent Charity Hospital, where he died in March, aged 76, of coronary insufficiency, Buerger's disease and glaucoma.

**Jacques Lewinski,** Brooklyn; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1912; died in the Bushwick Hospital March 5, aged 61, of coronary disease.

**William Bruce Lunsford,** Winchester, Mass.; Vanderbilt University School of Medicine, Nashville, Tenn., 1913; served during World Wars I and II; formerly on the staffs of various Veterans Administration hospitals; died March 6, aged 58, of hypertensive encephalopathy.

**Asa Calvier De McClellan,** Lockland, Ohio; Meharry Medical College, Nashville, 1909; died February 4, aged 67, of heart disease.

**Kenith Smith McIntyre** ✙ Hastings, Mich.; University of Michigan Medical School, Ann Arbor, 1925; served during World War II; past president of the Barry County Medical Society; affiliated with Pennock Hospital; died February 20, aged 47.

**Lewis Steele McQuade,** Quincy, Mass.; Tufts College Medical School, Boston, 1907; member of the American Medical Association; served during World Wars I and II; affiliated with the Veterans Administration Hospital; died in St. Margaret's Hospital, Boston, March 10, aged 66, of subacute virus hepatitis.

**Charles Allen McWilliams** ✙ Gulfport, Miss.; Medical Department of Tulane University of Louisiana, New Orleans, 1913; specialist certified by the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; served during World War I; on the staff of Memorial Hospital, where he died March 9, aged 61, of cerebral hemorrhage.

**Edwin Herman Maercklein,** Ashley, N. D.; Milwaukee Medical College, 1903; served during World War I; died in Veterans Administration Hospital, Minneapolis, March 7, aged 68, of bronchogenic carcinoma, squamous cell, with metastases to lung and kidney.

**Ralph Justin Malott** ✙ Scottsbluff, Neb.; Northwestern University Medical School, Chicago, 1920; on the staff of St. Mary's Hospital and the Western Nebraska Methodist Episcopal Hospital, where he died February 16, aged 56, of pulmonary edema.

**Elviro Mancusi-Ungaro** ✙ Newark, N. J.; University and Bellevue Hospital Medical College, New York, 1917; consulting pediatrician to the Essex County Sanatorium; on the staff of St. James and the American Legion hospitals; died March 9, aged 55, of portal cirrhosis.

**Kossuth A. Mayer,** Lower Peach Tree, Ala.; Memphis (Tenn.) Hospital Medical College, 1900; member of the American Medical Association; member of the board of censors of the Medical Association of the State of Alabama; died March 3, aged 71, of coronary thrombosis.

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**Harold Abiud Miller** ✠ Lansing, Mich.; University of Michigan Medical School, Ann Arbor, 1916; died in St. Lawrence Hospital March 2, aged 57, of hypertensive heart disease.

**William Mitchell,** Needham, Mass.; McGill University Faculty of Medicine, Montreal, Canada, 1894; died March 15, aged 76.

**Neil C. Monroe,** Rogers City, Mich.; Medical College of Indiana, Indianapolis, 1898; died February 26, aged 76, of cerebral thrombosis and cardiac embolism.

**Lucius D. Morgan,** Gladys, Va.; Medical College of Virginia, Richmond, 1903; member of the American Medical Association; died March 10, aged 78, of carcinoma of the kidney and bladder.

**Byron O. Mork Sr.,** ✠ Worthington, Minn.; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1907; on the staff of Worthington Hospital; died March 2, aged 81, of cerebral arteriosclerosis.

**Joseph Patrick Mulhern** ✠ Worcester, Mass.; Tufts College Medical School, Boston, 1918; fellow of the American College of Surgeons; served during World War I; examining physician for local board 164 during World War II; visiting surgeon, orthopedic service, St. Vincent Hospital; on the courtesy staff, orthopedics, Hahnemann Hospital; consulting surgeon, orthopedics, Worcester City Hospital, where he was president of the board of trustees, died March 6, aged 57, of aortic stenosis.

**Franklin Spilman Newell,** Boston; Harvard Medical School, Boston, 1896; professor of clinical obstetrics emeritus at his alma mater; member of the American Medical Association; member and past president of the American Gynecological Society; served as chief of staff and trustee of Boston Lying-in Hospital; died March 3, aged 77, of carcinoma of the stomach.

**David Nussbaum,** Hilltown, Pa.; Medizinische Fakultät der Universität Wien, Austria, 1906; specialist certified by the American Board of Otolaryngology; formerly on the faculty of the Graduate School of Medicine, University of Pennsylvania in Philadelphia, where he was on the staffs of Northern Liberties and Mount Sinai hospitals; died in Havertown, recently, aged 63, of coronary thrombosis.

**Madison Knox Patton,** Selma, Ala.; Medical Department of Tulane University of Louisiana, New Orleans, 1891; died February 16, aged 80, of chronic endocarditis and myocarditis.

**Samuel Charles Pierce,** Richmond, Calif.; University of Louisville (Ky.) Medical Department, 1900; died in Martinez, February 13, aged 78, of carcinoma of the pancreas, acute cholangitis and cholecystitis.

**Bradbury Norton Robinson,** St. Louis, Mich.; St. Louis University School of Medicine, 1908; died in St. Petersburg, Fla., March 7, aged 65, of heart failure.

**Orville Rockwell** ✠ Sunnyside, Wash.; University of Michigan Department of Medicine and Surgery, Ann Arbor, 1906; superintendent of the Nebraska Sanitarium in Lincoln from 1907 to 1913; chief surgeon, Boulder-Colorado Sanitarium from 1931 to 1936; died suddenly, March 4, aged 69, of coronary occlusion.

**Cuthbert Harry Rogerson** ✠ Baltimore; L.R.C.P., London and M.R.C.S., England, 1931; served as director of Seton Institute, formerly known as Mount Hope Retreat; at one time medical superintendent of Cassel Hospital, Swaylands, England; died February 10, aged 39, of glioblastoma.

**Carl Webber Rosenbloom,** Holyoke, Mass.; Tufts College Medical School, Boston, 1909; member of the American Medical Association; died March 2, aged 64, of bulbar paralysis.

**Frank Tipton Rudy,** Columbus, Ohio; Medical College of Indiana, Indianapolis, 1892; died in Grant Hospital March 2, aged 83, as the result of a fall.

**William Van Buren Saul,** Montpelier, Miss.; University of Louisville (Ky.) Medical Department, 1880; member of the American Medical Association; died February 4, aged 91.

**Arthur Sayer** ✠ New York; Columbia University College of Physicians and Surgeons, New York, 1919; associate professor of dermatology at the New York University College of Medicine; specialist certified by the American Board of Dermatology and Syphilology; served in the U. S. Navy during World War II; affiliated with the U. S. Naval Hospital in St. Albans, N. Y., Mount Sinai Hospital and Morrisania City Hospital; died February 22, aged 55, of coronary thrombosis.

**Samuel Benjamin Scholz** ✠ Jenkintown, Pa.; Denver and Gross College of Medicine, 1905; fellow of the American College of Physicians; veteran of the Spanish-American War; served as president of the Association of Life Insurance Medical Directors; retired medical director and formerly second vice president of the Penn Mutual Life Insurance Company in Philadelphia; died March 4, aged 70, of coronary occlusion.

**John Daniel Smyser,** Florence, S. C.; Maryland Medical College, Baltimore, 1912; member of the American Medical Association; served overseas during World War I; during World War II received congressional commendation for his services as regional director of Selective Service and procurement and assignment; colonel, medical reserve corps, U. S. Army, not on active duty; medical director and superintendent of Saunders Memorial Hospital; died February 15, aged 61, of coronary thrombosis.

**Berton A. Souders,** Cambridge, Ohio; Starling Medical College, Columbus, 1892; member of the American Medical Association; for many years member of the city school board; died March 3, aged 82, of cerebral hemorrhage.

**Henry Tucker Spelman,** Brooklyn; Columbia University College of Physicians and Surgeons, New York, 1907; member of the American Medical Association; on the staffs of Kings County Hospital and the Norwegian Hospital, where he died March 3, aged 64, of ulcerative colitis and heart disease.

**William H. Spiller,** New York; University of Virginia Department of Medicine, Charlottesville, 1894; served in the Spanish-American War, Boxer Rebellion and Philippine Insurrection; formerly superintendent of Lying-in Hospital of the city of New York; at one time affiliated with New York Hospital, where he died February 23, aged 76, of hypertensive and arteriosclerotic cardiovascular disease.

**Elizabeth Sweet,** Redlands, Calif.; Cornell University Medical College New York, 1901; died March 9, aged 78, of chronic myocarditis.

**Adolph Emil Voegelin** ✠ Detroit; Medico-Chirurgical College of Philadelphia, 1916; specialist certified by the American Board of Internal Medicine; fellow of the American College of Physicians; member of the American Heart Association; on the staff of Evangelical Deaconess Hospital; served during World War I; died February 22, aged 55, of myocardial infarction.

**Allan Estes Walker** ✠ Ferris, Texas; University of Texas School of Medicine, Galveston, 1933; served in British Ministry of Health from 1941 to 1942; officer during World War II; died March 3, aged 39, of thrombosis.

**John Henry Wallinga,** St. Paul; University of Minnesota Medical School, Minneapolis, 1919; secretary-treasurer of Samaritan Hospital; died in Belmond, Iowa, February 8, aged 58, in an automobile accident.

**Ancrum Waring Jr.,** ✠ Sanford, Mich.; Medical College of the State of South Carolina, Charleston, 1942; member of the Medical Society of the State of Pennsylvania; served during World War II and received battle stars for Normandy, France, Northern France, Ardennes and a silver star; on the staff of the Midland (Mich.) Hospital, died in the Saginaw (Mich.) General Hospital March 7, aged 32, of injuries received when a motorcycle on which he was riding skidded.

**Alfred Winslow Wheeler** ✠ Norfolk, N. Y.; Columbia University College of Physicians and Surgeons, New York, 1902; died February 28, aged 74, of acute coronary thrombosis.

**Roland Thatcher White** ✠ Orlando, Fla.; Chicago Homeopathic Medical College, 1886; died in the Florida Sanitarium and Hospital March 5, aged 84, of carcinoma of sigmoid with widespread metastases.

**Eugene Maximilian Wiedenmann,** Topeka, Kan.; Albert-Ludwigs-Universität Medizinische Fakultät, Freiburg, Baden, Germany, 1914; member of the American Medical Association and the American Psychiatric Association; assistant superintendent of Topeka State Hospital; died January 29, aged 59.

## DIED WHILE IN MILITARY SERVICE

**Thomas Hugh Spyker,** Plain City, Ohio; Ohio State University College of Medicine, Columbus, 1946; interned at the Shreveport Charity Hospital in Shreveport, La.; began active duty as a first lieutenant in the medical corps, Army of the United States, on May 15, 1947; promoted to captain; died in Tilton General Hospital, Fort Dix, N. J., March 27, aged 26.

# Foreign Letters

## ITALY

*(From Our Regular Correspondent)*

FLORENCE, March 31, 1949.

### Treatment of Diseases of the Liver

At the inauguration of the academic year of the Academy of Sciences of Ferrara, Professor Dogliotti, University of Turin, reported on "Treatment of Diseases of the Liver." The speaker discussed numerous important researches conducted in America, the results of which led to new problems in diagnosis and therapy of chronic hepatopathy with a cirrhogenous background. The most convenient treatment may be considered as follows: The amount of protein should be increased in the diet and the glycide rate should be maintained at a high level. According to some authors the amount of lipids should be reduced, but according to others it may vary around a relatively high level. In general, a decisively increased amount of alimentary calories should be given—i. e., from 3,000 to more than 3,500, with the patient at rest. In addition, a generous increase in lipotropic substances, particularly choline and methionine, is required. This therapy does not exclude the use of other means which experience has shown effective in hepatopathy, such as hepatic extracts, vitamin B complex, vitamin C and corticoadrenal extracts. Favorable statistics furnished by American schools have been confirmed by the results obtained in the institute which is under the direction of the speaker. It is, however, too early to draw definite conclusions in this highly complex field, in which symptomatology and therapy are not very clear.

### Association of Legal and Industrial Medicine

This association held a meeting in Naples under the chairmanship of Professor Palmieri. Sessa reported on his histologic research on rabbits and guinea pigs subjected to acute experimental intoxication with trinitrotoluene. The poison was administered by mouth on alternate days in doses of 0.20 to 0.50 Gm., with a total dose of 0.80 to 2 Gm. in four to eight days. Other animals were subjected to chronic intoxication with weekly doses of 0.01 Gm. to 0.02 Gm. with a total dose of 0.04 to 0.14 Gm. in twenty-four to fifty-two days.

On microscopic examination all the organs appeared injured, showing vascular congestion and occasional hemorrhages, and degenerative processes from turbid swelling to hyaline and fatty degeneration. The toxic process was characterized also by infiltration phenomena and mesenchymal reactions with noteworthy differences between the acute form, in which degenerative-necrotic elements prevailed and the chronic form, in which congestion and reaction were predominant.

During the various phases, changes were most evident in the kidney, liver and adrenal glands; next in order were those in the lungs, spleen, stomach and heart.

Prisco presented a report on cardiopathy. The statistics on the disabling and compensable morbidity from cardiopathy show among workmen an increase of about 2.65 per cent in the postwar period as compared with the prewar period. This increase, the speaker stated, was caused mostly by hardship among laborers, whose conditions of work had become particularly harassing. The speaker recommended a rigorous orientation concerning those suffering from cardiopathy, withdrawing them from heavy work which could disturb the circulatory compensation.

Graziani studied the oxygen consumption of the liver, of the kidney and of the bone marrow in the experimental intoxication by trinitrotoluene. Using Warburg's technic, he demonstrated a conspicuous increase in the consumption of oxygen by the liver and the bone marrow as compared with that in the control animals, while the respiratory quotient of the kidney was not modified. As far as the liver is concerned, the catalyzing action of oxidation was called on to explain the excess of the consumption of oxygen; with regard to the bone marrow, the increased consumption may depend on the medullary hyperplasia which was observed on microscopic examination.

### Peptic Ulcer and Electroshock

At the Association of Hospital Physicians of Genoa, Drs. Corbella and Piredda presented a preliminary note on the treatment of peptic gastroduodenal ulcer by means of electroshock.

The speakers recalled the first communications by Cushing in 1932, who had observed the occurrence of peptic ulcers as sequelae of surgical intervention on the base of the brain. There followed the investigations by Fulton, Hoff and Sheehan and by Roussy and Mossinger which resulted in the occurrence of bleeding ulcers in the gastroduodenal mucosa as sequelae of lesions produced in the diencephalon and in the prefrontal cortex of experimental animals.

The speakers recalled the symptoms of peptic gastroduodenal ulcer by which it resembles syndromes due to dysfunction of encephalic centers. They reported on electroshock therapy of 12 patients with gastroduodenal ulcer which had been demonstrated on roentgenologic examination. In all the subjects thus treated the painful symptoms and the dyspeptic disturbances subsided after the first treatment, and after the third treatment at the latest. The improvement was accompanied by a pronounced reduction of the free and combined hydrochloric acid. In a second report the speakers will present the late results of this therapeutic trial.

## THE NETHERLANDS

*(From Our Regular Correspondent)*

AMSTERDAM, April 26, 1949.

### Numerus Clausus or Numerus Fixus?

In the annual assembly of the Society of Friends of the University of Amsterdam the former President, Prof. J. J. van Loghem, gave a talk on the problem of the overcrowding of the universities. He treated this problem especially from the medical point of view. At this time there are 6,700 medical students—i. e., more than the total number of the medical profession in Holland. The medical faculties are overtaxed; consequently the quality of the medical training is in danger.

Professor van Loghem pointed out that numerus clausus—the university admits a limited number of students—is an attractive measure from the point of view of the professors and of the students admitted. On the other hand, it is an unsocial measure, as it does not reckon with the needs of the community. The speaker considered it preferable for the Government to fix each year a number representing the doctors expected to be wanted in the near future and to bring up the equipment of the faculties to this level. For this number Professor van Loghem coined the word numerus fixus, a conception intrinsically different from numerus clausus.

### Low Mortality Figures

Professor René Sand, the Belgian pioneer of social medicine, considers the low mortality figures of his Dutch neighbor in *Bruxelles Médical*. As important causal factors he mentions the Dutch law on infectious diseases, the splendid nursing and educational work of the Green, White and White-Yellow Crosses, the organization of the national campaign against tuberculosis, the schools for social workers, the drinking water policy, the system of social insurance, the housing law and the nutrition of the population. Even in 1930 the children of the unemployed in Holland showed normal development.

This subject is also treated in the "Epidemiological and Vital Statistics Report of the World Health Organization." An article by Dr. Stowman on "The Declining Deathrate" characterizes

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the Netherlands as "a class by itself, having the lowest general death rate in the world, in spite of its high birth rate which increases the age groups under 1 year having a high mortality risk. In 1947 the death rate was only 8.1 per 1,000, in 1948 7.4 per 1,000. It had never previously been considered possible to attain such low general death rates in a population of nearly ten millions without striking peculiarities in regard to economic or age constitution. An intensive investigation of this phenomenon and its possible underlying causes may well lead to useful results."

### Two New Medical Journals

An editorial in the *Nederlandsch Tijdschrift voor Geneeskunde* gives a hearty welcome to two new periodicals, both of them quarterly journals: *Archivum Chirurgicum Neerlandicum* and *Documenta Neerlandica et Indonesica de Morbis tropicis.*

The former is published by a Collegium chirurgicum representing general surgery, urology, chest surgery, neurosurgery, plastic surgery and anesthesia. The board of editors is made up of four professors of surgery (Amsterdam, Leyden, Utrecht, Groningen), with Prof. I. Boerema as chairman and Dr. H. R. Bax (Arnhem) as secretary. The first number contains eight original articles, excellently illustrated, all in English.

The new *Quarterly Journal of Tropical Medicine and Hygiene* (this is its subtitle) is published by a special foundation, Prof. J. E. Dinger (Leyden) being the chairman of the managing committee. Prof. N. H. Swellengrebel (Amsterdam) is the chairman of the editorial board and Dr. Ch. W. F. Winckel is the editor.

In his introduction Professor Swellengrebel lays stress on the fact that, although the scientific achievements of the Dutch in the Netherlands Indies have been rather creditable as far as quality is concerned, it is to be regretted that they have neglected to render these achievements intelligible to their colleagues abroad. The appearance of this journal in English shows their intention of mending their ways in the future.

### Centenary of the Medical Association

Next July the Netherlands Medical Association, which has its headquarters in Amsterdam, will celebrate the hundredth anniversary of its foundation. Eighty per cent of the medical profession are members of the association, constituting three subdivisions: the general practitioners, the specialists and the medical officers.

In Holland the ratio of physicians to the population is 89: 100,000; the analogous numbers for the United States is 104. The celebration in July will last three days. Its program contains a two day scientific congress, an automobile rally for doctors on their way to Amsterdam, a reception by the municipality, a performance in the municipal theater, a medical-historical exhibition and many other entertainments. The board of the association expects many guests from all parts of the world.

## BUENOS AIRES

*(From Our Regular Correspondent)*

Feb. 26, 1949.

### Coca Chewing

The Society for Forensic Medicine and Toxicology in Buenos Aires voted unanimously that it is erroneous to admit that chewing coca leaves is useful or indispensable to life in the Andean altitudes. Medical observations have repeatedly shown that the white men who live at the same altitudes—with few exceptions—do not chew, with the consequence that they work much better. However, it must be recognized that the "coqueo" is an old and deeply rooted habit among the Andean Indios. Chewing coca leaves day after day and in the accustomed quantities results in chronic intoxication, which contributes much to the physical and mental degeneration of the Indian race. The final goal must be the suppression of this habit, but the practical proceeding must be gradual, together with and during a definite improvement of the general living conditions for the native populations. It was noted that the resolution was voted on just at the moment when the United Nations are investigating the effect of chewing coca leaves on the inhabitants of certain regions of Latin America.

### Thoracolumbar Sympathectomy in Hypertension

Drs. A. C. Taquini, A. Villamil, J. R. E. Suárez and J. M. González Fernández determined the blood volume in 5 hypertensive persons (3 of grade II, 2 of III) before and after thoracolumbar sympathectomy. They found an increase due to elevation of plasma and globular volume, but no significant modification of the extracellular liquid. In almost all cases the venous pressure did not vary. The circulation time remained unaltered in 3 cases and was prolonged in 2. Serum proteins remained within normal limits. Seventeen to one hundred and thirty-seven days after the second operation the minute volume was diminished in the 3 cases of degree II, the medium arterial pressure somewhat diminished, the total peripheral resistance increased and the cardiac output diminished. In the cases of degree III the minute volume was slightly augmented and the medium arterial pressure and peripheral resistance diminished, while the cardiac output remained practically unchanged. Later on, eight months to two years after the second operation, the 3 patients of degree II and 1 of III showed a similar picture: the minute volume was like that before the operation, and the medium pressure, the peripheral resistance and the cardiac output showed values like those before the operation or somewhat less. In the other case of degree III the minute volume and the cardiac output decreased below the preoperative level while the medium pressure and the peripheral resistance increased, the latter above preoperative figures.

### Renal Lesions of Experimental Diabetes

Dr. V. G. Foglia, of the Houssay-Institute in Buenos Aires, together with Drs. R. E. Mancini and A. F. Cardozo, found that in extirpating 95 per cent of the pancreas of male and female rats, lesions appear only after two months, the glycemia remaining normal during this time; the same is the case after extirpation of more than 95 per cent (although hyperglycemia appears immediately). After the two months, the lesions are found in all of the rats; first an increase occurs in hyaline in the arterioles and the glomerular capillaries; later reticulin fibers appear in these vessels, and finally sclerosis. These glomerular lesions are diffuse and almost always serious, like those of diabetic patients, although without showing the hyaline masses.

### Congress of Ophthalmology

The fourth National Congress of Ophthalmology was held in Mar del Plata. Among those present were Drs. Castroviejo and Conrad Berens of New York, A. R. Beese from Columbia, G. A. Hanson of Seattle; also specialists from France, Spain and Switzerland and delegates from many Latin American countries. There were four exhibitions: a scientific one by the four Argentine universities, one of social work, made by the Ministry of Public Health, an industrial one, and one of books and periodicals. The chairman was the titular professor for ophthalmology of the University of La Plata, Dr. Diego M. Argüello. The main subject was "Eye Tumors."

### Causes of Death

In the city of Buenos Aires the figure for tuberculosis remained more or less the same: 2,735 in 1939 and 2,359 in 1947; that for cancer increased from 3,696 to 4,772 in 1947, but that for circulatory diseases increased steadily, from 5,698 in 1939 to 8,093 in 1947.

### Brief Items

The third South American Congress of Neurosurgery will be held in Buenos Aires in March 1949. The main subjects will be surgical treatment of epilepsy; hemostasis in neurosurgery, and lobectomies. The president is Prof. Dr. Ramón Carrillo, Minister of Health, who is titular professor of neurosurgery in Buenos Aires.

The prize Mariano R. Castex of the National Academy of Medicine of Buenos Aires has been granted to Drs. Egidio S. Mazzei and Diego Taylor Gorostiaga y Elyeser Magalhaes, for their paper "El embolismo pulmonar en clínica, obstetricia y cirugía."

## Correspondence

### ANTABUS® FOR ALCOHOLISM

*To the Editor:*—In THE JOURNAL, April 2, page 954, there is a note on antabus® entitled "Antabus for Alcoholism," written by Dr. J. Murray Scott, medical director of Ayerst, McKenna & Harrison, Ltd.

We wish to call attention to the fact that the Monsanto Chemical Company has been manufacturing ethyl thiurad,® which is chemically tetraethyl thiuram disulfide and referred to as antabus® by Dr. Scott, as an item of commerce for the rubber industry for a number of years. The chemical is an old one, and we also wish to call attention to the fact that Monsanto has been supplying experimental quantities of highly purified tetraethyl thiuram disulfide to responsible ethical pharmaceutic houses capable of conducting qualified experiments on its value in the treatment of alcoholism.

We too have recognized the sociologic significance of this development and have carefully screened requests for this material. It is interesting to note that our medical people had observed for some time that workers on this compound, as well as other chemicals for the rubber industry, developed intolerance to alcohol. We are glad that the Danish workers have carried out their work showing the possible medical value in the treatment of alcoholism.

Since the articles referred to by Dr. Scott have appeared in the literature, however, we have been supplying qualified groups of investigators requesting the material for pharmacologic and clinical purposes.

HAL G. JOHNSON, PH.D.
Monsanto Chemical Co.,
St. Louis.

### MEDICINE IN THE PANAMA CANAL ZONE

*To the Editor:*—I have recently returned from a trip to the Canal Zone as a consultant to the Medical Department of the United States Army. I visited the Gorgas Hospital at Ancon, the Army Hospital at Fort Clayton, the Naval Hospital at Coco Solo and the Army Hospital at Colon.

I was afforded every opportunity to study the ophthalmic care given the patients, who included Army and Navy personnel, their dependents and the civilian employees of the government. In ten days, packed with activities, the over-all impression that I have carried away is that of excellent care given the patients, the high professional quality of the medical officers responsible for this care, and their hunger for professional shop talk.

There are weak spots to be sure; it could be scarcely otherwise when we consider that the Medical Department is understaffed at the moment and contains a number of men who have but recently completed their internships. In spite of these shortages, which are not too serious, there is evident a desire by the medical officers to give the best they can and to keep their professional acumen and keenness to a high level.

The facilities that are supplied the ophthalmologists are equal to those in many large universities and clinics and better than some. I was also impressed with the care that is taken of these necessary tools for good work.

Gorgas Hospital is, of course, the major installation. There is an enormous quantity of clinical material and an exciting variety of rare and unusual cases seldom seen outside of large charity hospitals. The opportunity to study and learn is endless, and most of the doctors have taken advantage of this chance. The atmosphere of the place is more like that of a well run medical school and hospital than any Government hospital with which I am familiar. The library is superb and contains not only an adequate number of up-to-date medical textbooks and systems, but a much larger variety of the current medical journals than are usually found in a general hospital. The good will of the commanding officer and his obvious desire to provide the best tools with which the doctors can do their jobs, unhampered by rules, regulations and red tape, are reflected throughout the institution. The result is, naturally, a happy and peaceful aura about the place that makes for contented work.

To draw together the civilian and Army doctors in this manner is a thrilling experience and cannot help being beneficial to the patients, the medical officers and the civilian consultants alike. The Medical Department of the Army is to be congratulated for adopting this fine program.

DERRICK VAIL, M.D., Chicago.

### "LITTLE STROKES"

*To the Editor:*—Sophocles (C. 497 B. C.—405 or 406 B. C.) died suddenly and happily—probably from overexertion while giving a public reading of his tragedy "Antigone" or/and from overexcitement and joy when he was proclaimed victor in a contest, after reading the play or, as is altogether likely, from coronary thrombosis or a "little stroke" in his advanced old age, rather than from choking on an unripe grape!

Of interest, now, is the fact that Sophocles 2,400 years ago knew of, and wrote about, "little strokes." In his "Oedipus Tyrannus," 961, Sophocles says, "A little stroke puts aged bodies to sleep." Thus Walter C. Alvarez, of the Mayo Clinic, has recently revived the term "little stroke!"

I might add, too, that the old experienced navigator or pilot Phrontis, son of Onetor and Menelaus' boatman (Homer's Odyssey, Book III), dropped dead suddenly from overexertion with the steering oar of the moving ship (against the storming winds) within his hands. This sudden death was caused by coronary thrombosis or perhaps by Sophocles' "little stroke" rather than by Phoebus Apollo's gentle darts! Archangelus Piccolhomini (1525-1586) is of the opinion that "the obstruction of the little cord or vessel [or "nerve"] which goes to the heart, suddenly brought on, is the cause from which some persons go suddenly and unexpectedly out of this world."

HYMAN I. GOLDSTEIN, M.D., Camden, N. J.

### INCIDENCE OF UNDULANT FEVER

*To the Editor:*—To determine the incidence of undulant fever in a private practice in the Stock Yards District of Chicago, we studied the blood samples of 100 consecutive patients between the months of June 1948 and January 1949. Of these 57 per cent were female and 43 per cent male, the ages varying from 19 to 63. All laboratory tests were done by the Division of Laboratories of the State of Illinois, Department of Public Health. Only one reaction was positive, and this in a dilution of 1 to 5,120, and 1 person had recovered from acute brucellosis five years previously.

FREDERICK STENN, M.D.
JOSEPH PLESTINA, M.T.
Chicago.

# Medical Examinations and Licensure

## COMING EXAMINATIONS AND MEETINGS

### NATIONAL BOARD OF MEDICAL EXAMINERS

NATIONAL BOARD OF MEDICAL EXAMINERS: *Parts I and II.* Various Centers. June 20-22, Sept. 12-14. *Part III.* June, various centers. Exec. Sec., Mr. E. S. Elwood, 225 S. 15th St., Philadelphia 2.

### EXAMINING BOARDS IN SPECIALTIES

AMERICAN BOARD OF ANESTHESIOLOGY, INC. *Written.* Various Centers. July 15. *Oral.* Oct. 16-20. Sec., Dr. Curtiss B. Hickcox, 745 Fifth Ave., New York 27.

AMERICAN BOARD OF INTERNAL MEDICINE: *Oral.* Philadelphia, June 1-3. *Written.* Oct. 17. Asst. Sec.-Treas. Dr. W. A. Werrell, 1 Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: *Oral.* Chicago, June 1949. Sec., Dr. W. J. German, 310 Cedar Street, New Haven, Conn.

AMERICAN BOARD OF OPHTHALMOLOGY: *Oral.* New York, June 11-15; St. Louis, Oct. 15-19; Boston, December. Sec., Dr. S. J. Beach, 56 Ivie Rd., Cape Cottage, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY. *Part II,* New York City, Jan. 1950.: Final date for filing application for Part II is Aug. 15. Address: Sec.-Treas., Dr. Harold A. Sofield, Room 1856, 122 S. Michigan Ave., Chicago.

AMERICAN BOARD OF OTOLARYNGOLOGY: Chicago, Oct. 4-7. Sec., Dr. D. M. Lierle, University Hospital, Iowa City.

AMERICAN BOARD OF PEDIATRICS: *Written.* Under local monitors, June 24. *Oral.* Cleveland, Sept. 16-18; New York City, Oct. 21-23; Chicago, Dec. 9-11. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PHYSICAL MEDICINE. Philadelphia, June 4-5. Sec., Dr. R. L. Bennett, 30 N. Michigan Blvd., Chicago.

AMERICAN BOARD OF PLASTIC SURGERY: Examinations are given in June and November of each year in the home town of applicants. Sec., Treas., Dr. Louis T. Byars, 400 Metropolitan Bldg., St. Louis, Mo.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY, INC. *Special Examination,* October. Place to be announced. Final date for filing application is July 15. December, New York City. Sec. Dr. F. J. Braceland, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY. Atlantic City, June 2-4. Sec., Dr. B. R. Kirklin, 102-110 Second Ave., S.W., Rochester, Minn.

AMERICAN BOARD OF SURGERY: *Written.* Various Centers, October 26. Final date for filing application is July 1. Sec., Dr. J. Stewart Rodman, 225 S. 15th St., Philadelphia.

AMERICAN BOARD OF UROLOGY: *Written,* December. *Oral and Clinical.* Chicago, Feb. 11-15. Final date for receipt of case histories is Sept. 1, 1949. Sec., Dr. Harry Culver, 7935 Sunnyside Road, Minneapolis 18, Minn.

### BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 28-30. Sec., Dr. D. G. Gill, 519 Dexter Ave., Montgomery.

ARKANSAS: * Little Rock, June 9-10. Sec., Dr. L. J. Kosminsky. Texarkana. *Eclectic.* Little Rock, June 9-10. Sec., Dr. C. H. Young, 1415 Main St., Little Rock.

CALIFORNIA: *Examination.* San Francisco, June 21-23. Sec., Dr. Frederick N. Scatena, 1020 N St., Sacramento.

COLORADO: * *Examination.* Denver, June 20-22. Sec., Dr. W. W. King, 831 Republic Bldg., Denver.

CONNECTICUT: * *Examination.* Hartford, July 1. Secretary to the Board, Dr. Creighton Barker, 258 Church Street, New Haven.

DELAWARE: Dover, July 12-14. Sec., Dr. J. S. McDaniel, 229 South State St., Dover.

FLORIDA: * *Examination,* Jacksonville, June 26-28. Sec., Dr. Frank D. Gray, 12 N. Rosalind Ave., Orlando.

GEORGIA: *Examination.* June 8-9, Atlanta and Augusta. *Reciprocity.* Atlanta, June. Sec., Mr. R. C. Coleman, 111 State Capitol, Atlanta.

GUAM: *Endorsement.* Agana, Last Friday of each month. Sec., Capt. C. K. Youngkin, Dept. of Public Health, Guam. % F.P.O., San Francisco, Calif.

HAWAII: * *Examination.* Honolulu, July 11-14. Sec., Dr. S. E. Doolittle, 881 S. Hotel St., Honolulu.

IDAHO: Boise, July 11-13. Sec., Miss Estella S. Mulliner, Bureau of Occupational Licenses, 355 State House, Boise.

ILLINOIS: Chicago, June 28-30. Superintendent of Registration, Mr. Fred W. Ruegg, Capitol Building, Springfield.

INDIANA: *Examination.* Indianapolis, June 21-23. Sec. Board of Medical Registration and Examination. Dr. Paul R. Tindall, 416 K. of P. Bldg., Indianapolis.

IOWA: * *Examination.* Iowa City, June 13-15. Sec., Dr. M. A. Royal, 506 Fleming Bldg., Des Moines.

KANSAS: Kansas City, June 1-2. Sec., J. F. Hassig, 905 North 7th St., Kansas City, Kans.

KENTUCKY: *Examination.* Louisville, June 15-17. Sec., Dr. Bruce Underwood, 620 S. 3rd St., Louisville 2.

LOUISIANA: New Orleans, June 6-8. Sec., Dr. Roy B. Harrison, 1507 Hibernia Bank Bldg., New Orleans.

MAINE: Augusta, July 5-6. Sec., Dr. Adam P. Leighton, 192 State St., Portland.

MARYLAND: *Examination.* Baltimore, June 21-24. Sec., Dr. Lewis P Gundry, 1215 Cathedral St., Baltimore. *Homeopathic.* Baltimore, June 14-15. Sec., Dr. John A. Evans, 612 West 40th St., Baltimore.

MASSACHUSETTS: *Written.* Boston, July 12-15. Sec., Dr. George L. Schadt, 413 E. State House, Boston.

MICHIGAN: * *Written.* Detroit and Ann Arbor, June 13-15. Sec., Dr. J. Earl McIntyre, 203 Hollister Bldg., Lansing.

MINNESOTA: * Minneapolis, June 21-23. Sec., Dr. Julian F. DuBois, 230 Lowry Medical Arts Bldg., St. Paul 2.

MISSISSIPPI: Jackson, June 21-22. Asst. Sec., Dr. R. N. Whitfield, State Board of Health, Jackson.

MISSOURI: *Examination.* St. Louis, June 8-10. Exec. Sec., Mr. John A. Hailey, Box 4, Jefferson City.

MONTANA: Helena, Oct. 3-5. Sec., Dr. Otto G. Klein, First National Bank Bldg., Helena.

NEBRASKA: * *Examination.* Omaha, June 6-8. Dir., Bureau of Examining Boards, Mr. Oscar F. Humbie, 1009 State Capitol Building, Lincoln 9

NEW HAMPSHIRE: Concord, Sept. 8-9. Sec., Dr. J. S. Wheeler, 107 State House, Concord.

NEW JERSEY: *Examination.* Trenton, June 21-24. Sec., Dr. E. H Hallinger, 28 West State Street, Trenton 8.

NEW YORK: Albany, Buffalo, New York and Syracuse, June 28-July 1. Sec., Dr. Jacob L. Lochner, 23 South Pearl St., Albany.

NORTH CAROLINA: *Examination.* Raleigh, June 23-25. Sec., Dr. Ivan Proctor, 226 Hillsboro St., Raleigh.

NORTH DAKOTA: * *Written,* Grand Forks, July 5-7. *Reciprocity,* Grand Forks, July 8. Sec., Dr. C. J. Glaspel, Grafton.

OHIO: *Examination.* Columbus, June 15-18. *Endorsement,* Columbus, July 5. Sec., Dr. H. M. Platter, 21 W. Broad St., Columbus.

OKLAHOMA: * Oklahoma City, June 8-9. Sec., Dr. Clinton Gallaher, 813 Braniff Bldg., Oklahoma City.

OREGON: * *Examination.* Portland, July 7-9. *Reciprocity.* Portland, July 22. Exec. Sec., Mr. Howard I. Bobbitt, 609 Failing Building, Portland.

PENNSYLVANIA: *Examination.* Philadelphia and Pittsburgh, July. Acting Sec., Mrs. B. G. Steiner, 351 Education Bldg., Harrisburg.

PUERTO RICO: San Juan, Sept. 6-10. Sec., Dr. Luis Cueto Coll, Box 3717, Santurce.

RHODE ISLAND: * *Examination.* Providence, July 7-8. Chief, Mr. Thomas B. Casey, 366 State Office Bldg., Providence.

SOUTH CAROLINA: *Examination.* Columbia, June 27-29 *Endorsement.* Columbia, June 27-28, Aug. 1, Sept. 5 and Oct. 3. Sec., Dr. N. B. Heyward, 1329 Blanding St., Columbia.

SOUTH DAKOTA: * *Examination.* Pierre, July 19. Sec., Dr. G. J. Van Heuvelen, Capitol Bldg., Pierre.

TEXAS: *Examination.* Austin, June 16-18. Sec., Dr. M. H. Crabb, 209 Medical Arts Bldg., Fort Worth 2.

UTAH: *Examination.* Salt Lake City, July 13-15. Sec., Dept. of Registration, Miss Rena B. Loomis, 324 State Capitol Bldg., Salt Lake City.

VERMONT: Burlington, June 21-23. Sec., Dr. F. J. Lawliss, Richford.

VIRGINIA: *Examination.* Richmond, June 17-18. *Reciprocity.* Richmond, June 16. Dr. K. D. Graves, 631 First St., S.W., Roanoke.

WASHINGTON: * Seattle, July. Sec., Mr. Edward C. Dohm, Department of Licenses, Olympia.

WISCONSIN: * *Examination.* Milwaukee, June 28-30. Sec., Dr. C. A. Dawson, Tremont Bldg., River Falls.

WYOMING: Cheyenne, June 20. Sec., Dr. Franklin D. Yoder, Capitol Bldg., Cheyenne.

* Basic Science Certificate required.

### BOARDS OF EXAMINERS IN THE BASIC SCIENCES

ALASKA: Feb. 1950. Sec., Dr. C. Earl Albrecht, Box 1931, Juneau.

ARIZONA: Tucson, June 21. Sec., Mr. Francis A. Roy, Science Hall, University of Arizona, Tucson.

COLORADO: *Examination.* Denver, June 1-2. Sec., Dr. Esther B Starks, 1459 Ogden St., Denver.

CONNECTICUT: New Haven, June 11. Exec. Asst., State Board of Healing Arts, Miss Mary G. Reynolds, 110 Whitney Ave., New Haven 10.

FLORIDA: *Examination.* Gainesville, June 11. Sec., Mr. M. W. Emmel, University of Florida, Gainesville.

MICHIGAN: *Examination.* Detroit and Ann Arbor, Oct. 14-15. Sec., Miss Eloise LeBeau, 101 N. Walnut St., Lansing 15.

MINNESOTA: Minneapolis, June 7-8. Sec., Dr. Raymond N. Bieter, 105 Millard Hall, University of Minnesota, Minneapolis.

OREGON: Portland, June 18, Sept. 3 and Dec. 3. Sec., Mr. Charles D Byrne, State Board of Higher Education, Eugene.

SOUTH DAKOTA: Vermillion, June 3-4. Dr. G. M. Evans, 310 E. 15th St., Yankton.

TENNESSEE: Memphis, July 8-9. Sec., Dr. O. W. Hyman, 874 Union Ave., Memphis 3.

WISCONSIN: Milwaukee, June 4, Sept. 24 and Dec. 3. Sec., Prof. W. H. Barber, Ripon College, Ripon.

# Bureau of Legal Medicine and Legislation

## MEDICOLEGAL ABSTRACTS

**Governmental Hospitals: Validity of Rules Fixing Standards for Practitioners Therein.**—The plaintiff physician filed suit to restrain the defendant, Hamilton County Hospital, from interfering with, or discriminating against, him in his right to practice and perform his professional duties in the hospital. From a judgment for the physician, the hospital appealed to the appellate court of Indiana (81 N. E. [2d] 699; J. A. M. A. 139:251 [Jan. 22] 1949) and eventually to the Supreme Court of Indiana.

On Sept. 9, 1947, the board of trustees of the defendant hospital adopted certain rules regulating the qualifications which a physician must possess in order to practice medicine, surgery and obstetrics in the hospital. It was provided that "the Resident Active Medical Staff, which shall include all the physicians having an unlimited license to practice medicine in the state of Indiana and having membership in Hamilton County Professional organization of fully licensed physicians having the largest number of such physicians residing in Hamilton County" shall make up the membership of the Active Medical Staff of the hospital. "(*d*) 2. All appointments to the Staff and assignments to services shall be made by the Board of Trustees but only upon the recommendation of the Active Medical Staff. The Board of Trustees will either accept the recommendation of the medical staff or refer it back for further consideration with a statement of its reasons for such action: When final action has been taken by the governing body the superintendent will be authorized to transmit its decision to the candidate and to the chief of staff. . . ." Other rules provided that in order for a physician to practice in the hospital he either must be a member of this medical staff or must have a member of the medical staff associated with him in the treatment of his patient. A surgeon desiring to practice surgery in the hospital but not being a member of the surgical staff was required to be a member of the Active Medical Staff and, in addition, was required to "(*b*) have a certificate of internship showing one year's service as an intern in a hospital approved by the Council on Medical Education and hospitals of the American Medical Association. (*c*) In addition to intern training required under (*b*) he shall have had not less than three years of surgical training which meets the approval of the American College of Surgeons."

The plaintiff graduated from Indiana University School of Medicine in 1938 and practiced medicine in the state of Indiana from that time until June 1942, when he entered the army. He was placed on the army inactive list in January 1945 and became a resident of Noblesville, Ind., about January 1947. He was not a member of the Hamilton County Medical Society and was therefore denied membership on the Active Medical Staff of the defendant hospital. Furthermore, he did not have the intern training required to practice surgery in the hospital. He was therefore refused permission to practice medicine or surgery in the hosptial.

To require membership of the plaintiff in the resident active medical staff of the defendant hospital before permitting him to practice in the hospital, said the Supreme Court, would be a reasonable requirement if such staff were provided for by reasonable rules of the hospital, or the Board of Health through its Council, as provided by the Indiana Statutes. The present rules, however, provide that the hospital can appoint new members to its staff only on recommendation of its staff. It would seem by this rule, the Supreme Court continued, that recommendation to membership may be rejected by the board, but that no one shall be made a member of the staff without such recommendation. This is an unreasonable requirement, as by it the hospital delegates to its staff a virtual veto of its right to perform one of its duties. By this arrangement the staff dictates what physicians may practice in the hospital. In so holding we are aware that courts of at least one other jurisdiction have approved of staff selection in public hospitals by invitation from their staff. (Selden v. City of Sterling, 45 N. E. [2d] 329; J. A. M. A. 121:886 [March 13] 1943). With this holding we cannot agree.

It will be further noted, the Supreme Court continued, that by the involved rules, the plaintiff's right to practice in the hospital is not only conditioned on his being a member of the staff but also on his being a member of the Hamilton County Medical Society, an extragovernmental agency. His admission to this society depends entirely on the sole determination of the society. Whether he could ever become a member depends on conditions beyond his control. By this rule the hospital again delegates its power to determine what physicians may use its facilities. It amounts to a preference in favor of the society and a discrimination against those physicians who by choice or otherwise are not members of the same.

It is our conclusion, said the Supreme Court, that the complaint stated facts entitling the plaintiff to some relief; namely, the right to practice general medicine, excluding surgery, in the hospital, without being a member of the staff as here constituted, as membership on this staff can be increased only on recommendation of the staff and is limited to members of the Hamilton County Medical Society. It is our further opinion that the plaintiff is not qualified, under the valid portions of the rules now in force, to perform surgery in the hospital. We therefore affirm that portion of the judgment of the trial court which would prohibit the plaintiff from doing surgery and reverse that portion of the judgment which would prohibit the plaintiff from practicing medicine in the hospital other than surgery. Judgment was entered accordingly. *Hamilton County Hospital v. Andrews, 84 N.E. (2d) 469 (Ind., 1949).*

# Medical Motion Pictures

## FILM REVIEWS

**Surgical Division of a Patent Ductus Arteriosus.** 16 mm., color, silent, 625 feet (1 reel), showing time twenty-five minutes. Produced in 1948 by Mervin La Rue & Co., Chicago. Prepared by and procurable on loan from Willis J. Potts, M.D., The Children's Memorial Hospital, 707 Fullerton Avenue, Chicago 14.

The motion picture reviews briefly the essential signs and symptoms for a diagnosis of patent ductus arteriosus and emphasizes the diagnostic importance of a continuous "humming top" murmur. The surgical technic of division of a patent ductus by means of a new clamp is shown in detail. The basic feature of the clamp is embodied in rows of tiny teeth in the opposing jaws; when closed on the ductus, the teeth are embedded in the wall and will not slip. One clamp is placed on the aortic end of the ductus and another is placed on the pulmonary end. The ductus is cut and the stumps sutured with a double row of dekanatel® silk on a curved no. 9 atraumatic needle. The color photography ranges from fair to excellent. A few scenes are overexposed, and closer views of the author's method of clamping, dividing and suturing the patent ductus arteriosus would have improved this section of the picture. When considered in its entirety, the film is far superior to the average picture on this subject. It is highly recommended for showing to surgeons who are particularly interested in this type of surgery and residents working in a hospital where this work is being done.

**Vaginal Hysterectomy.** 16 mm., silent, color, 475 feet (1 reel), showing time seventeen minutes. Produced by Dwinnell Grant Productions. Prepared in 1948 by and procurable on loan from Charles C. Weitzman, M.D., 847 Eastern Parkway, Brooklyn.

This motion picture attempts to demonstrate the author's operative technic in a vaginal hysterectomy with repair of cystocele and rectocele. Illustrative anatomic drawings are interspersed throughout the picture, some of which are misleading and do not give a clear concept of the topographic site. The operative field is unreasonably obscured by blood and the operator's hands, so that the steps of the operation are not easily discernible. This is a record type film having a minimum of teaching value. It is not recommended. The photography is poor to good.

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# Current Medical Literature

## AMERICAN

The Association library lends periodicals to members of the Association and to individual subscribers in continental United States and Canada for a period of three days. Three journals may be borrowed at a time. Periodicals are available from 1938 to date. Requests for issues of earlier date cannot be filled. Requests should be accompanied by stamps to cover postage (6 cents if one and 18 cents if three periodicals are requested). Periodicals published by the American Medical Association are not available for lending but can be supplied on purchase order. Reprints as a rule are the property of authors and can be obtained for permanent possession only from them.

Titles marked with an asterisk (*) are abstracted below.

### American Journal of Psychiatry, New York

**105**:481-560 (Jan.) 1949. **Partial Index**

Extramural Medical Care and National Resources. P. R. Hawley. —p. 481.
Public Mental Hospitals In England. A Survey. D. Pratt.—p. 485.
Patient Population Distribution in Mental Hospitals In United States. S. Leibman and R. L. French.—p. 489.
Prophylactic Electroshock. J. J. Geoghegan and G. H. Stevenson.—p. 494.

### American Journal of Tropical Medicine, Baltimore

**28**:755-918 (Nov.) 1948. **Partial Index**

Field Experiments with Chloroquine Diphosphate. D. A. Berberian and E. W. Dennis.—p. 755.
Teaching of Malaria Diagnosis. A. J. Walker.—p. 777.
Evaluation of Complement Fixation Tests for Malaria. A. Harris and L. M. Reidel.—p. 787.
Transient Urticaria in Malaria. M. Kissin and R. J. Adleman.—p. 797.
Clinical Manifestations and Treatment of Epidemic Amebiasis Occurring in Occupants of Mantetsu Apartment Building, Tokyo, Japan. C. Davis and L. S. Ritchie.—p. 817.
*Use of Streptomycin in Cultivation of Endameba Histolytica from Stools. C. L. Spingarn and M. H. Edelman.—p. 825.
Cutaneous Leishmaniasis in the United States: Report of Case in Veteran. S. H. Auerbach and R. R. Buchholz.—p. 831.
Present State of Chagas' Disease Surveys in Chile. A. Neghme and J. Román.—p. 835.
Nomenclature of Agent of Murine Typhus. H. Mooser.—p. 841.
Treatment of Q Fever with Streptomycin: Case Report. C. G. Spicknall, L. L. Terry and R. J. Huebner.—p. 845.
Q Fever: Serologic Survey of Bovine Serums in United States. C. C. Shepard.—p. 849.
Experimental Histoplasmosis: Portal of Entry of Fungus. R. M. Allen. —p. 857.
Studies on Incidence of Trichiniasis in Mississippi: Preliminary Report. T. J. Brooks Jr., J. W. Ward and T. M. Holder.—p. 863.
Laboratory Evaluation of DDT Residual Effectiveness Against House Flies, Musca Domestica. R. W. Fay, A. J. Buckner and S. W. Simmons.—p. 877.

**Streptomycin in Cultivation of Endameba Histolytica.**—In a previous study Spingarn and Edelman found that streptomycin prolonged the survival of cultures of trophozoites of Endameba histolytica. This effect was associated with bacterial inhibition. The favorable influence of streptomycin in prolonging the viability of trophozoites suggested that the drug might also prove valuable in starting cultures from cysts of E. histolytica found in stools. When they used a standard technic, their attempts to obtain cultures of trophozoites from stools containing cysts were usually failures. When streptomycin was added to the cultures at the time of inoculation with feces containing cysts, trophozoites were found with great regularity. The authors describe the method they used and the results obtained. They found that the addition of streptomycin in doses ranging from 1.0 to 10.0 mg. per cubic centimeter of serum-saline overlay favored the production of cultures of trophozoites from cysts of E. histolytica present in stools. The drug produced varying degrees of bacterial inhibition, and the growth of Bacillus hominis was suppressed. They believe that further experiments relating to the effect of antibiotics on E. histolytica may eventually provide a simple, reliable method for culturing trophozoites from cyst-containing stools. Their results confirm observations that there is considerable variability in the conditions required for the excystation and growth of E. histolytica in a particular specimen. By using a wide range of doses of streptomycin and, perhaps, penicillin as well, it may be possible to control the nature and density of bacterial flora in such a manner as to be able to culture E. histolytica cysts from stools in every instance. This is an essential prerequisite for the use of a cultural method for diagnosis when microscopic studies reveal no or doubtful evidence of amebiasis.

### American Practitioner, Philadelphia

**3**:261-324 (Jan.) 1949

Angina Pectoris: Symptoms and Differential Diagnosis. M. Plotz.—p. 261.
Evaluation of Present Forms of Treatment of Polycythemia Rubra Vera. L. O. Jacobson and T. R. Smith.—p. 267.
Present Status of Treatment of Toxic Goiter. W. O. Thompson.—p. 271.
Complications and Precautions in Blood Transfusion Therapy. E. E. Muirhead and J. M. Hill.—p. 275.
Dietary Cholesterol: Its Role in Atherosclerosis. B. A. Sachs.—p. 284.
Dermatologic Problem of Adolescent. L. Hollander.—p. 290.
Clinical Significance of Rumination. J. N. Dambassis.—p. 309.
Thrombophlebitis in Lower Extremity. J. E. Summers.—p. 315.
Propylthiouracil in Treatment of Angina Pectoris: Preliminary Report. R. L. Fisher and M. Zukerman.—p. 318.

**Clinical Significance of Rumination.**—Dambassis reports 9 cases of rumination in 4 multiparous women, 2 obese and 2 not, between the ages of 38 and 60, in 1 thin girl aged 22, in 1 obese man aged 45, in 2 boys aged 6 and 10 respectively and in 1 girl aged 9. The incidence was higher for women than for men. The hereditary factor was not present, although "ruminant families" have been described. Rumination is not a physiologic phenomenon. Hiatus hernia was present in 2 of the author's adult patients. Such conditions are favorable substrata for the development of rumination. The 3 children had a history suggestive of a low grade congenital circular muscle pyloric hypertrophy which commonly subsides in the first six months, sometimes leaving a certain degree of pylorospasm capable of causing squeezing contraction of the stomach musculature and elevation of the fundic pressure. In one of the middle-aged women aerophagia was the chief complaint, associated with temporary pylorospasm resulting in an increase of the fundic pressure. The girl aged 22 had an irritable colon; her case was considered among the reflex conditions in which anomalous impulses are brought about and result in a regional gastrospasm or an incompetence of the cardia. In another middle-aged woman rumination was due to incompetence of the cardia, which had undergone an overrelaxation after having passed its culminant point of spasticity. The case of the obese man aged 45 was typical as that of a heavy and hasty eater and drinker who ruminated from his childhood, carrying over possibly a conditioned reflex probably caused by the infantile gluttony observed in some children. Treatment of rumination consists in reeducation of the patient and the appropriate therapy of the underlying cause. A bland diet is indicated. Coffee, tea and alcohol should be discarded. Some drugs such as phenobarbital, papaverine, calcium carbonate, bitter digestives and any glandular preparation are indicated.

### Archives of Ophthalmology, Chicago

**40**:101-238 (Aug.) 1948

Necrosis of Intraocular Tissues. B. Samuels.—p. 101.
Incidence of Defective Color Vision Among Psychotic Patients. L. H. Hardy, Gertrude Rand and M. Catherine Rittler.—p. 121.
Preplacement of Air in Cyclodialysis. S. Rome and R. Koff.—p. 134.
Deep Keratitis Associated with Atypical Lichen Planus: Report of Case. J. Goldsmith.—p. 138.
Aid in Detecting Trachoma-Like Inclusion Bodies in Conjunctiva. M. Bodian.—p. 147.
Occlusion of Cilioretinal Artery. L. M. Levitt.—p. 152.
*"Silent" Dacryocystitis. F. H. Theodore.—p. 157.
History of Dartmouth Eye Institute. H. M. Burian.—p. 163.
Di-Isopropyl Fluorophosphate (DFP) in Treatment of Glaucoma: Further Observations. I. H. Leopold and P. R. McDonald.—p. 176.
Lattice Type of Hereditary Corneal Degeneration: Report of Five Cases, Including One of Child of Two Years. F. C. Stansbury.—p. 189.

**"Silent" Dacryocystitis.**—Theodore says that dacryocystitis is generally described as a chronic inflammation of the lacrimal sac due to stenosis of the nasolacrimal duct. The stenosis develops as a result of inflammation of the nasal mucosa extending by continuity to the mucous membrane of the nasolacrimal duct. A mucopurulent or purulent discharge is present, which flows into the conjunctival sac on pressure. Sometimes a mucocele develops. The condition known as acute dacryocystitis is more properly designated as acute peridacryocystitis. It occurs when the organisms present in chronic dacryocystitis

penetrate the submucous tissue and invade the wall of the sac itself. The "acute" inflammation is secondary to chronic dacryocystitis. These two types of inflammation of lacrimal sac appear to be the only ones generally accepted, but there exists a third type, an incipient, mild, low grade dacryocystitis in which obstruction is not important. The author reports 7 cases in which a mild type of dacryocystitis, usually mucoid in character, was the unsuspected cause of persistent conjunctivitis or of unexplained tearing. This "silent" type of dacryocystitis is overlooked if investigation of the tear passages is limited only to a determination of patency. If the lacrimal washings are collected and examined both clinically and bacteriologically, the finding of mucus or of pus containing pathogenic bacteria will indicate the presence of "silent" dacryocystitis. Once the diagnosis was established and treatment instituted, the conjunctivitis, which in almost every case of the present series had existed for months, subsided in a matter of weeks, recovery paralleling the clearing of the lacrimal washings. Experience suggests that this low grade type of mucous dacryocystitis is not uncommon and, if not recognized, may eventually lead to more obvious inflammatory changes in the lacrimal passages.

## Archives of Surgery, Chicago

**57**:443-612 (Oct.) 1948

*Treatment of Thyroiditis. G. Crile Jr.—p. 443.
Surgical Management of Branchiogenic Cysts and Sinus Tracts. C. W. McLaughlin Jr.—p. 450.
Early Diagnosis and Roentgen Manifestations of Obstruction of Small Bowel. C. J. Hunt.—p. 460.
Potassium Metabolism in Immediate Postoperative Period. R. E. L. Berry, Vivian Iob and K. N. Campbell.—p. 470.
*Lymphatic Spread of Carcinoma of Breast. C. W. Monroe.—p. 479.
Experiences with Dragstedt Skin-Covered Ileostomy. G. B. Sanders. —p. 487.
Value of Transmetatarsal Amputations in Management of Gangrene of Toes. W. Furste and L. G. Herrmann.—p. 497.
Role of Antibiotics in Masking Inflammatory Processes. A. R. Curreri, E. R. Schmidt and J. T. Mendenhall.—p. 513.
Preoperative Place of Streptomycin in Operations on Bowel. H. S. Morton and F. Smith.—p. 520.
Inguinal and Femoral Hernioplasty: Anatomic Repair. C. B. McVay. —p. 524.
Glomus Tumors: Summary of 15 Cases. K. E. Lemmer.—p. 531.
Keloids and Hypertrophic Scars. H. M. Trusler and T. B. Bauer. —p. 539.
Parenteral Use of Water, Dextrose, Electrolytes, Fat and Vitamins. W. G. Maddock.—p. 553.
Lesions of Patellar Cartilage as Cause of Internal Derangements of Knee. C. W. Peabody and F. P. Walsh.—p. 589.
Arterial Blood Supply of Common Bile Duct. T. C. Douglass and W. W. Cutler.—p. 599.

**Treatment of Thyroiditis.**—According to Crile there exist three main clinical types of thyroiditis: (1) the subacute (pseudotuberculous or giant cell) variety, (2) struma lymphomatosa (Hashimoto's thyroiditis) and (3) Riedel's struma. In 2 cases of subacute thyroiditis and 2 cases of struma lymphomatosa proved by biopsy, roentgen therapy was followed by complete resolution of the palpably enlarged thyroid. Three patients with proved Riedel's struma were not benefited by roentgen therapy. Crile stresses that roentgen therapy is the treatment of choice for subacute thyroiditis, and thyroidectomy is rarely, if ever, indicated. When the diagnosis of struma lymphomatosa is made before operation, roentgen therapy should be given a trial, but if struma lymphomatosa is recognized at the time of operation a very conservative resection of both lobes of the thyroid is recommended. In Riedel's struma, roentgen therapy is of little or no value, and it is unwise, unnecessary and often dangerous to attempt to remove the entire lobe. If the onion-like concentric laminations in the fibrous tissue surrounding the central degenerating adenoma can be found, these avascular planes can be followed by blunt dissection and the core of the lobe shelled out without disturbing its capsule. After this procedure the symptoms are relieved and there is no further proliferation of fibrous tissue.

**Lymphatic Spread of Carcinoma of Breast.**—Monroe made a detailed pathologic study of 87 breast specimens removed at radical mastectomy. The location of the lymph nodes has been accurately charted and each of the lymph nodes examined microscopically. The study indicates that the greater the number of lymph nodes removed in the operative specimen, the greater the patient's chances for freedom from recurrence.

## Cancer Research, Baltimore

**8**:349-396 (Aug.) 1948

Ascorbic Acid Content in Human Cancer Tissue. A. Góth and I. Littmann.—p. 349.
Method of Staining Nucleoli of Cells in Fresh Benign and Malignant Tissues. W. W. Ayres.—p. 352.
Diagnosis and Treatment of Primary Ovarian Carcinoma with Special Reference to Radiation Therapy. J. H. Freed and E. P. Pendergrass. —p. 361.
Lack of Extractable Carcinogens in Skin of Patients with Multiple Precancerous Keratoses of Actinic Origin. F. E. Mohs.—p. 371.
Effect of Carcinogenic Compounds on Ascorbic Acid Content of Liver in Mice and Rats. M. Daff, C. Hoch-Ligeti, E. L. Kennaway and M. M. Tipler.—p. 376.
Increased Weight of Liver in Wistar Albino Rats with Induced and Transplanted Tumors. Eleanor H. Yeakel.—p. 392.
Influence of Growth and Adrenocorticotropic Hormones on Body Composition of Hypophysectomized Rats. Choh Hao Li, Miriam E. Simpson and H. M. Evans.—p. 71.
Renal Excretion of Water and Antidiuretic Substances in Patients with Hepatic Cirrhosis and Rats with Dietary Liver Injury. C. A. Hall, B. Frame and V. A. Drill.—p. 76.
Androgen: Ketosteroid Ratios of Rabbit Urine. C. T. Davis, C. R. Slater and B. Krichesky.—p. 83.
Changes in Distribution and Concentration of Alkaline Phosphatases in Tissues of Rat After Hypophysectomy or Gonadectomy, and After Replacement Therapy. E. W. Dempsey, R. O. Greep and Helen Wendler Deane.—p. 88.

## Endocrinology, Springfield, Ill.

**43**:355-460 (Dec.) 1948

Cytologic Examination of Uterine Growth During Pregnancy. C. A. Salvatore.—p. 355.
Use of Stilbestrol Inhibited Males as Test Animals for Gonadotrophic Hormones. A. V. Nalbandov and G. J. Baum.—p. 371.
Formation of Secondary Deciduomata in Spayed Mice and Lactating Rats. P. Constantinides.—p. 380.
Progesterone and Estrogen in Experimental Control of Ovulation Time and Other Features of Estrous Cycle in Rat. J. W. Everett.—p. 389.
Bio-Assay of Caloriganic Substances Using Tadpoles of Xenopus Laevis. C. F. Hamilton, A. Albert and M. H. Power.—p. 406.
Further Studies on Protective Power of Adrenal Extract and Steroids Against Toxic Agents. Lena A. Lewis and I. H. Page.—p. 415.
Growth Inhibition in Bone and Bone Marrow Following Treatment with Adrenocorticotropin (ACTH). B. L. Baker and D. J. Ingle.—p. 422.
Influence of Quantitative Thyroprotein Treatment of Hens on Length of Incubation Period and Thyroid Size of Chicks. R. S. Wheeler and E. Hoffmann.—p. 430.
Effect of Adrenalectomy and Adrenal Cortical Hormone upon Formation of Antibodies. J. S. Thatcher, B. C. Houghton and Carolyn H. Ziegler. —p. 440.

## Illinois Medical Journal, Chicago

**94**:337-390 (Dec.) 1948

Clinical Interpretation of Sternal Puncture. P. L. Bedinger and L. R. Limarzi.—p. 351.
Present Management of Peptic Ulcer. J. B. Kirsner and W. L. Palmer. —p. 357.
Delay in Treatment of Cancer. Faye E. Bates and I. M. Ariel.—p. 361.
Follow-Up Studies of Patients with Pre-Frontal Lobe Lobotomy. J. Coheen.—p. 366.
*Mass X-Ray Examination Using Miniature Films. C. Hall.—p. 369.
Roentgen Ray Aspects of Malignancies of Small Intestines. E. L. Rypins. —p. 372.
Toothpick in Ascending Colon. C. W. Olsen, E. G. Johnson and G. Bilek. —p. 374.

**Mass Roentgen Examination.**—Hall says that of 107,005 miniature roentgenograms taken, 1,726 disclosed signs suggestive of tuberculosis. Of these, 1,366 proved to be minimal lesions, 259 moderately advanced and 101 far advanced. The miniature roentgenogram is a tool that does not replace either the standard roentgenogram or the medical training and experience of the practitioner. The physician plays an all-important part in the mass survey program. He gets the results of this detection process, and the ultimate diagnosis of tuberculosis or of other pathologic conditions is up to him. A study of results of tuberculosis control programs in the past indicates that much time and energy probably have been devoted to the wrong population groups. Tuberculosis is not a disease found commonly in children. The mass survey also indicates that the prevalence of tuberculosis increases with age. The survey should not be conducted in grade schools, but should be concentrated among industrial and other general adult population groups. We can protect children from tuberculosis by detecting tuberculosis among the parents. An adult population free of tuberculosis will result in a young generation free of infection. Tuberculosis is spread almost entirely by adults. If all tuber-

culous adults could be found, isolated, treated and the disease arrested, the next generation would have practically no source of infection, and tuberculosis would become a relatively infrequent disease.

## Journal of Bacteriology, Baltimore

**56:**699-842 (Dec.) 1948. **Partial Index**

Consequences of Mutation During Growth of Biochemical Mutants of Escherichia Coli. I. Pattern of Adaptation of Histidineless Cultures. F. J. Ryan and Lillian K. Schneider.—p. 699.

Enzymatic Studies on Mechanism of Resistance of Pneumococcus to Drugs. J. S. Gots and M. G. Sevag.—p. 709.

*Circulin, an Antibiotic From Member of Bacillus Circulans Group: I. Bacteriologic Studies. Charlotte McLeod.—p. 749.

Morphologic Characteristics of Certain Cultured Strains of Oral Spirochetes and Treponema Pallidum as Revealed by Electron Microscope. E. G. Hampp, D. B. Scott and R. W. G. Wyckoff.—p. 755.

Control of Salmonella Infections in Colonies of Mice. C. A. Slanetz. —p. 771.

Micro-Organisms in Cecal Contents of Rats Fed Various Carbohydrates and Fats. H. Nath, V. H. Barki, W. B. Sarles and C. A. Elvehjem. —p. 783.

Analysis of Action of Proflavine on Bacteriophage Growth. Ruth A. C. Foster.—p. 795.

**Circulin, an Antibiotic.**—McLeod says that a new antibiotic has been obtained from broth cultures of a mucoid variant of Bacillus circulans. This substance is active against both gram-positive and gram-negative bacteria and against fungi. It is bactericidal as well as bacteriostatic, and the activity is not appreciably reduced in the presence of blood serum. Circulin is hemolytic and extremely toxic. Although it is unsuitable for parenteral administration, limited trials indicate that it has possible value in the treatment of bacterial and fungous infections of the skin. Efforts are now being made to reduce the toxicity of circulin.

## Journal of Infectious Diseases, Chicago

**83:**207-300 (Nov.-Dec.) 1948

Further Observations on Complement Fixation in Typhus Fever. Wei-T'Ung Liu, Huei-Ching Chang and P'Ei-Jen Wang.—p. 207.

Further Studies on Occurrence and Distribution of Salmonella Types in United States. P. R. Edwards, D. W. Bruner and Alice B. Moran. —p. 220.

Experiments with Bovine Strain of Leptospira Isolated from Human Patient. H. Bernkopf, L. Olitzki, L. A. Stuczynski and others. —p. 232.

Immunology of Certain Mouse-Adapted Poliomyelitis Virus Strains when Cultivated in Embryonated Eggs. H. M. Powell and W. A. Jamieson. —p. 238.

Physiologic Studies on Spore Formation in Clostridium Botulinum. E. S. Wynne.—p. 243.

Ability of Plasmodium Lophurae to Acquire Resistance to Chlorguanide, Camoquin and Chloroquine. P. E. Thompson.—p. 250.

Studies on Action of Penicillin: VII. Development of Penicillin Resistance by Meningococcus in Vivo. C. P. Miller and Marjorie Bohnhoff. —p. 256.

Effect of Quinine Treatment of Host on the Carbohydrate Metabolism of Malarial Parasite Plasmodium Gallinaceum. J. W. Moulder.—p. 262.

Growth Response of Leuconostoc to Nicotinic Acid, Nicotinamide, and Some Related Compounds. S. A. Koser and G. J. Kasai.—p. 271.

In Vitro Cultivation of Rat Leprosy Organism. R. Ashbel and A. Poljakoff.—p. 279.

Hemagglutination by Influenza Virus: I. Modification of O Phase of Influenza A Virus. B. A. Briody.—p. 283.

Id.: II. Existence of Two Phases of Influenza B Virus. B. A. Briody. —p. 288.

Id.: III. XO Phase of Influenza A Virus. B. A. Briody.—p. 293.

## Journal-Lancet, Minneapolis

**69:**1-32 (Jan.) 1949

Value of Estrogen Therapy in Treatment of Varicose Veins Complicating Pregnancy. H. O. McPheeters.—p. 2.

Postpartum Hemorrhage. R. J. Moe.—p. 5.

Prepartum Care. G. Brown.—p. 7.

Management of Neglected Transverse Presentation by Waters Extraperitoneal Cesarean Section: Report of 2 Cases. C. W. Seibert.—p. 9.

Puerperal Sepsis: Case Report. J. F. Bicek.—p. 11.

Basal Temperature Records in Obstetrics and Gynecology. M. B. Sinykin.—p. 13.

*Peritoneal Irrigation in Treatment of Severe Oliguria Caused by Transfusion Reaction. F. J. McCaffrey.—p. 17.

Concomitant Extra-Uterine and Intra-Uterine Pregnancy. W. P. Sadler. —p. 22.

Massive Hemorrhage Into Gastro-Intestinal Tract in Last Trimester: Case Report. M. T. Mitchell.—p. 26.

**Peritoneal Irrigation in Oliguria Caused by Transfusion.**—McCaffrey reports a woman, aged 40, in whom renal insufficiency due to a transfusion reaction developed. Caudal analgesia and renal decapsulation failed to alter the progress of the uremic syndrome, but peritoneal irrigation effected an immediate dramatic lowering of the blood metabolites with great clinical improvement in the patient. The return of renal function is not believed due directly to the use of peritoneal lavage but it is felt that the lowering of the blood metabolites in the short span of eighty-two hours of lavage halted the progress of the uremia for a sufficient period to enable the kidneys to regain their normal functions. The method is recommended as worthy of consideration in any case of uremia that threatens to have a fatal outcome.

## New Jersey Medical Society Journal, Trenton

**45:**569-622 (Dec.) 1948

Anticoagulant Treatment of Venous Thrombosis. A. J. D'Alessandro. —p. 572.

Infectious Hepatitis and Liver Function. M. Magnes.—p. 580.

Hysterectomy: Pathologic Analysis of 2000 Uteri Removed at Operation. S. J. Rose.—p. 583.

Surgical Complications of Pregnancy. J. R. Willson.—p. 589.

Cancer Problem in Proctology. F. S. Forte.—p. 594.

## Northwest Medicine, Seattle

**47:**863-932 (Dec.) 1948

Industrial Health Blueprints. H. R. Hennessy.—p. 883

Newer Procedures in Diagnosis of Occupational Diseases. C. M. McGill. —p. 885.

Extracapsular Fracture of Hip; Improved Plate for Fixation. W. B. McKibben.—p. 888.

Traumatic Rupture of Pancreas. R. S. Smith.—p. 892.

Spontaneous Rupture of Abdominal Aortic Aneurysm Into First Portion of Jejunum with Fatal Intestinal Hemorrhage. K. M. Clisby and P. Grabicki.—p. 895.

## Pennsylvania Medical Journal, Harrisburg

**52:**185-344 (Dec.) 1948

Open Pages in Neurology. H. H. Reese.—p. 201.

Recent Advances in Pre- and Postoperative Care. J. E. Rhoads.—p. 207.

The Healing Mission. W. H. Fineshriber.—p. 210.

Roentgen Diagnosis of Otitis Media and Mastoiditis in Infancy and Early Childhood. B. R. Young.—p. 213.

## Surgery, Gynecology and Obstetrics, Chicago

**88:**1-144 (Jan.) 1949

Apocrine Tissue, Chronic Cystic Mastitis and Sweat Gland Carcinoma of Breast. J. F. Higginson and J. R. McDonald.—p. 1.

Vaginal Operations for Cystocele, Prolapse of Uterus, and Stress Incontinence. W. Shaw.—p. 11.

*Experimental Pulmonary Embolism. W. D. Holden, B. W. Shaw, D. B. Cameron and others.—p. 23.

*Nature of Lateral "Aberrant" Thyroid Tumors. S. Warren and J. D. Feldman.—p. 31.

*Evaluation of Skin Grafting in Technic of Radical Mastectomy in Relation to Local Recurrence of Carcinoma. H. Conway and C. G. Neumann.—p. 45.

Obstructed Uterine Cervix. G. F. Melody.—p. 50.

Technic of Surgical Division of Patent Ductus Arteriosus. O. H. Wangensteen, R. L. Varco and I. D. Baronofsky.—p. 62.

Fractures of Upper End of Radius and Ulna. F. D. Dickson.—p. 69.

One Hundred Cases of Congenital Absence of Vagina. A. L. Bryan, J. A. Nigro and V. S. Counseller.—p. 79.

Carcinoma Developing in Chronic Draining Cutaneous Sinuses and Fistulas. A. K. McAnally and M. B. Dockerty.—p. 87.

*Effect of Intravenous Glucose and Amino Acids on Glycosuria and Urinary Output in Humans. C. E. Lockhart and R. Elman.—p. 97.

Fetal Mortality and Morbidity in Cesarean Section. S. Pedvis, J. K. L. Irwin and N. W. Philpott.—p. 103.

Prolapse of Redundant Gastric Mucosa. A. M. Cove and W. C. Curphey. —p. 108.

Indurated Leg and Leg Ulcers: Clinical Study of Their Etiology and Treatment. H. Mahorner.—p. 115.

**Experimental Pulmonary Embolism.**—Holden and his co-workers attempted to determine whether or not pulmonopulmonary, pulmonovagal depressor and pulmonocoronary reflexes contributed to the death of animals subjected to massive pulmonary embolism. Pulmonary embolism closely simulating that occurring in human beings was produced experimentally in dogs. No evidence was obtained from these experiments to support the supposition that pulmonopulmonary, pulmonocoronary or pulmonovagal depressor reflexes contribute to the death of dogs after massive pulmonary embolism. It is suggested as a result of this work that the use of papaverine in the treatment of massive pulmonary embolism is without benefit and may be harmful. The constant absence of postembolic thrombosis in the pulmonary arteries of the heparinized animals suggests that the early intravenous administration of heparin to patients may be of great value.

**Lateral "Aberrant" Thyroid Tumors.**—Warren and Feldman feel that in regard to the tumors of thyroid tissue in the lateral regions of the neck three possibilities have to be considered: (1) lateral thyroid tumors originate in thyroid tissue which is separated from the thyroid gland by defective embryogenesis and in the majority of cases metastasize to the thyroid; (2) tumors in thyroid and aberrant thyroid tissue represent multicentric neoplastic growth in a single type of embryonal rest; (3) they are early metastases from a tumor of the thyroid gland and become clinically apparent before the tumor of the thyroid manifests itself. The authors aimed to determine what features can be considered as evidence for one or another mode of origin. They analyzed the lateral thyroid tumors received in the laboratory of the New England Deaconess Hospital over a period of nineteen years. There were 63 cases diagnosed as lateral aberrant thyroid tumor among approximately 20,000 surgically removed thyroids. In 57 of these the clinical diagnosis of lateral thyroid tumor was confirmed by histologic examination. In 49 of the 57 cases there was an associated thyroid cancer. In the remaining 8 cases the thyroid was not received in the laboratory, either because it was removed elsewhere or because it was regarded as uninvolved. The histology of the tumor in the thyroid and in the lateral masses of the neck was identical in all but 1 instance. In 40 of the 57 cases the lateral tumors were found to be metastases to cervical lymph nodes. In the remaining 17 cases there was no microscopic evidence that the lateral tumors were either metastatic or derived from embryonal rests. Thus the data indicate that most if not all lateral thyroid tumors of the neck are metastases from cancers of the thyroid. These neoplasms tend to occur in a younger age group than does cancer or thyroid disease. The presenting symptom is usually only a swelling or nodule in the neck. The disease often recurs locally unless completely eradicated. Follow-up observations must be made over decades rather than years.

**Skin Grafting in Radical Mastectomy.**—This study by Conway and Neumann is based on 255 patients on whom radical mastectomy was performed for carcinoma of the breast. The shortest follow-up was five years. Special attention has been given to the relation of the use of a skin graft to local recurrence. In 188 cases in which a graft was employed, there were 40 instances of local recurrence (21 per cent), whereas in 67 cases of closure without a graft, there were 4 instances of local recurrence (6 per cent). However, the size of the tumor at the time of operation had an important bearing on the incidence of local recurrence. In the smallest tumors the rate of local recurrence was 4 per cent, whereas in the largest tumors the rate of recurrence was nearly 50 per cent. Local recurrence had a bearing on the length of survival. In the 125 patients surviving more than five years, local recurrence developed in 1.6 per cent, whereas in the 130 patients surviving less than five years the rate of recurrence was 32 per cent. Of the 40 instances of local recurrence following grafting, 27 appeared as solitary nodules in the immediate vicinity of the graft whereas only 13 appeared within the grafted area or as multiple metastases both surrounding and within the grafted area. This situation gives rise to the thought that more radical excision of skin might give further protection against local recurrence. Since the rate of local recurrence seems to be closely related to the size of tumor at the time of operation, it seems likely that local recurrence in the form of solitary nodules outside the area of grafting is related to insufficient removal of skin. The suggestion is therefore made that the excision of skin in radical mastectomy be more radical. With the improved methods of skin grafting now available, it seems indefensible that surgeons should not remove a truly wide area of skin at the time that radical mastectomy for carcinoma is carried out. The larger the tumor the greater the need for wide excision of skin.

**Effect of Intravenous Dextrose and Amino Acids on Urinary Output.**—Lockhart and Elman gave one hundred and four timed and controlled 1 liter injections of dextrose solutions intravenously to 32 selected adults. These subjects were patients in the general surgical wards who were either awaiting plastic or other elective procedures or had had their operation previously and were about to be discharged. The dextrose solutions were administered intravenously in the usual amount (1 liter) at rates ranging from 0.35 to 3.1 Gm. per kilogram per hour. The glycosuria resulting from each injection and the degree of diuresis were measured. The following solutions were utilized: 5 per cent dextrose in water; 5 per cent dextrose in isotonic sodium chloride solution; 10 per cent dextrose in water; 10 per cent dextrose in isotonic sodium chloride solution; 5 per cent amigen® in 5 per cent dextrose; 5 per cent amigen® in 10 per cent dextrose; 5 per cent pure amino acids in 5 per cent dextrose; 15 per cent dextrose in water; 15 per cent dextrose in 5 per cent amigen®; 15 per cent dextrose in 5 per cent pure amino acids; isotonic sodium chloride solution. The maximum speed of injection of dextrose without production of glycosuria was found to approximate 0.5 Gm. per kilogram per hour. This is much lower than the rate of 0.85 Gm. per kilogram per hour found by Woodyatt and his co-workers. In clinical usage this slower rate of injection should be used when dextrose is administered intravenously even to patients in a good state of health, in order to avoid glycosuria and associated diuresis. Urinary output was considerably reduced when isotonic sodium chloride was present in the intravenous solution. Higher concentrations of dextrose tended to produce more diuresis than lower concentrations, and the amount of diuresis tended to increase with the increased rates of administration. Evidence was obtained that the addition of hydrolyzed protein (amigen®) or pure amino acids to the dextrose solutions increased the rate of utilization of dextrose by the tissues. This was shown by a lower blood sugar level and less glycosuria when amino acids were present than when solutions of dextrose alone were given at the same rate.

## Tennessee State Medical Assn. Journal, Nashville

**41**:437-476 (Dec.) 1948

Indications for Splenectomy with Case Reports. E. R. Campbell.—p. 437.
Preliminary Report on Production of Rh Hapten for Treatment of Erythroblastotic Mothers. C. G. Ransom, A. R. Ransom and Jane Ransom.—p. 447.

## Virginia Medical Monthly, Richmond

**75**:595-649 (Dec.) 1948

Specialization: Its Advantages and Abuses. B. R. Kirklin.—p. 597.
Management of Esophageal Lesions. W. P. Longmire Jr.—p. 601.
*Influenza Virus Vaccine, Types A and B: Experience with it in Cold Prevention. W. B. Blanton and A. K. Sutphin.—p. 607.

**Influenza Virus Vaccine and Prevention of Colds.**—The purpose of this study by Blanton and Sutphin was to determine whether or not in a selected civilian group a stock influenza virus vaccine of types A and B could influence the number and severity of the whole group of acute infections of the upper respiratory tract. Approximately 1,400 industrial workers and college students in Richmond were given 1 cc. of influenza virus vaccine in the fall of 1946. An additional 583 male employees of the same company received the vaccine elsewhere in the state. No epidemic of influenza occurred in Virginia during the period of study. No convincing evidence was obtained to show that the common cold is influenced by this type of vaccine.

## West Virginia Medical Journal, Charleston

**44**:325-357 (Dec.) 1948

Natural History and Treatment of Infectious Hepatitis. P. H. Long.—p. 325.
Modern Trends in Surgical Treatment of Cancer of Lower Gastro-Intestinal Tract. F. W. Rankin.—p. 329.
Management of Menopause with Psychosomatic Aspects. E. Novak.—p. 334.

## Wisconsin Medical Journal, Madison

**47**:1145-1268 (Dec.) 1948

President's Annual Dinner Address. W. D. Stovall.—p. 1163.
Bladder Tumors: Their Diagnosis, Treatment, and Prognosis. J. C. Sargent.—p. 1166.
Strangulated Inguinal Hernia in Man of 88 Years: Operation and Recovery. V. S. Falk Jr.—p. 1172.
Placenta Accreta. B. E. Urdan and A. M. Kurzon.—p. 1174.
Management of Surgical Diabetic Patient. R. S. Baldwin.—p. 1177.
Acute Intestinal Obstruction in Patient Over 60 Years: Review of 80 Cases. H. B. Haley and A. S. Jackson.—p. 1180.
Bronchopulmonary Segments and Variations in Pulmonary Vascular Patterns. A. B. Appleton.—p. 1185.

## FOREIGN

An asterisk (*) before a title indicates that the article is abstracted. Single case reports and trials of new drugs are usually omitted.

### British Journal of Cancer, London

**2**:177-308 (Sept.) 1948

Racial and Social Incidence of Cancer of Uterus. E. L. Kennaway. —p. 177.
Statistical Report on 2529 Cases of Cancer of Breast. W. L. Harnett.—p. 212.
*Duodenal Spread of Pyloric Carcinoma. J. H. Fodden.—p. 239.
Squamous Cell Carcinoma Occurring in Asbestosis of Lung. R. J. R. Cureton.—p. 249.
Hemagglutination by Extracts of Tumors and of some Normal Tissues. M. H. Salaman—p. 253.
Estrogen-Induced Fibroids for Thoracic Serosa. S. Bruzzone, H. Elgueta, R. Iglesias and A. Lipschutz.—p. 267.
Role of Initiating and Promoting Factors in Pathogenesis of Tumors of Thyroid. W. H. Hall.—p. 273.
Effects of Thiol-Compounds on Tumor Induction by Carcinogenic Hydrocarbons. H. G. Crabtree.—p. 281.
Further Experiments in Mice with p-Diazoaminobenzene. A. H. M. Kirby. —p. 290.
Action of 2-Aminofluorene in Three Pure Strains of Mice. A. H. M. Kirby.—p. 294.
Metabolism of 3:4-Benzpyrene in Human Beings After Intravenous Injection. S. Iversen.—p. 301.

**Duodenal Spread of Pyloric Carcinoma.**—After reviewing the literature on duodenal immunity from cancerous permeation, Fodden presents his investigations on the frequency and manner of spread of the neoplasm into the first part of the duodenum in 50 cases of pyloric carcinoma. Sixteen cases showed that such an invasion of the duodenum had occurred, the invasion being more widespread and destructive in necropsy cases than in surgical cases. In 5 out of the 9 surgical specimens showing such duodenal involvement, cancer cell groups were seen at the edge of the duodenal resection. Progression of the growth occurred mainly through the lymphatics of the duodenal wall, and demonstrated an anastomosis between the pyloric lymphatic plexuses and those of the first part of the duodenum. In a smaller proportion of cases the pyloric neoplasm invaded the duodenal tissues directly. It was felt that the familiar macroscopic check to pyloric cancers at the duodenum was due to the duodenal mucous membrane and the layer of Brunner glands. Microscopically, these were the only tissues which appeared to resist the spread and destructive effects of the growth.

### British Journal of Radiology, London

**22**:1-60 (Jan.) 1949

Mackenzie Davidson Memorial Lecture, 1948. ". . . The Future Comes Apace, What Shall Defend the Interim? . . ." E. R. Carling.—p. 1.
*Radiological Diagnosis of Intestinal Obstruction by Means of Direct Radiography. J. H. Middlemiss.—p. 11.
Some Aspects of Mucosal Pattern in Diagnostic Study of Carcinoma of Stomach. G. Steiner.—p. 25.
Investigation Into Some Factors Affecting X-Ray Dose Distribution and Its Measurement. R. Oliver and L. A. W. Kemp.—p. 33.
Report on Installation of Ten Gramme Teleradium Unit. J. H. Martin, T. J. Tulley and E. B. Harriss.—p. 44.
Further Survey of Radiation Sickness with Particular Reference to Its Treatment by Pyridoxine. L. M. Shorvon.—p. 49.

**Diagnosis of Intestinal Obstruction by Direct Radiography.**—Middlemiss investigated the part which radiology can play as a diagnostic measure in 151 cases of suspected mechanical intestinal obstruction and in 37 cases of postoperative distension. The distended bowel contains gas and fluid, and these two static elements separate to form fluid levels in the most dependent loops of the bowel. Gas shadows appear on roentgenograms as less opaque shadows than those of neighboring tissues or fluids. Roentgenographic technic therefore must be directed toward the demonstration and utilization of these gas shadows as a contrast medium. A routine technic of a supine and an erect roentgenogram of the abdomen using a posteroanterior projection where possible and using intensifying screens and a moving grid at an anode-film distance of 36 to 48 inches (91.4 to 121.9 cm.) is recommended. The appearances of mechanical obstruction of the bowel are as follows: stasis within the bowel as shown by the presence of fluid levels, and distension of bowel by gas. The site of the obstruction can be localized as being distal to the most distal part of the distended bowel. Thus obstructions of the small bowel can be labeled high, mid or low obstructions. Obstructions of the large bowel can usually be localized more accurately; care must be taken not to diagnose an obstruction of the large bowel with an incompetent ileocecal valve as an obstruction of the small bowel. Volvulus, intussusception and perforation of a gas-containing viscus are conditions which may produce roentgenologic signs recognizable on scout survey films. Negative roentgen findings must be evaluated with reserve. Mechanical obstruction may still exist in the absence of positive roentgenologic evidence. It is of utmost importance to differentiate between adynamic obstruction, localized and generalized, and mechanical obstructions, as the early recognition of the latter in postoperative cases may be a life-saving measure. Closest liaison between the clinician and the radiologist is emphasized.

### Indian Medical Gazette, Calcutta

**83**:353-398 (Aug.) 1948. **Partial Index**

Report on Epidemic of Anterior Poliomyelitis in Nicobar Islands. S. H. Moses.—p. 355.
*Extrapleural Plombage with Lucite Spheres. N. L. Bordia.—p. 363.
Aneurysm of Thoracic Aorta. A. K. Nandi.—p. 365.
Lymphadenoma of Salivary Glands. B. P. Tribedi and A. R. Roy. —p. 367.

**Extrapleural Filling with Lucite® Spheres.**—Bordia shows that the use of extrapleural filling or plugging is not a new procedure and that with the advent of antibiotics this operation is again being used more frequently. In the search for a suitable substance for extrapleural filling the plastic methyl methacrylate (lucite®) has been tried; since the solid substance proved too heavy, hollow spheres have been used. The author cites American workers who have used this filling substance and discusses the indications and contraindications to its use. He outlines the technic of the operation and the postoperative course. This method may be extremely useful in the management of tuberculosis in India. The ease with which it can be undertaken makes it suitable for the conditions there. He believes it will replace thoracoplasty in the vast majority of cases.

### Lancet, London

**2**:997-1023 (Dec. 25) 1948

Aims of Medicine. E. D. Adrian.—p. 997.
Drug Sensitizing Organism to Ethyl Alcohol. J. Hald and E. Jacobsen. —p. 1001.
*Treatment of Alcoholism with Sensitizing Drug. O. Martensen-Larsen. —p. 1004.
Peritoneal Effusion as Complication of Artificial Pneumoperitoneum. R. C. Cohen.—p. 1006.
*Hypertrophy of Pylorus in an Adult with Massive Eosinophil Infiltration and Giant-Cell Reaction. H. J. Barrie and J. C. Anderson.—p. 1007.
Calciferol by Intramuscular Injection. Teresa Lightbound.—p. 1010.
Pethidine in Obstetrics: Review of 153 Cases. P. J. O'Reilly.—p. 1012.

**Sensitizing Drug Against Alcoholism.**—Martensen-Larsen points out that the discovery by Hald and Jacobsen, that the intake of tetraethylthiurnamdisulfide (antabus®) sensitizes the organism to even moderate doses of alcohol, makes it possible to develop a medical treatment for alcoholism. Concurrently with the examination of the pharmacologic effects of this substance, Martensen-Larsen has studied the clinical effects of the drug on alcoholic addicts. From December 1947 to May 1948, 83 patients have been treated. So far no harmful systemic effects on liver, heart, kidney or blood-forming organs have been observed; nor have any untoward side effects been noted. The treatment has produced satisfactory results in 74 of the patients. The remaining 9 have lacked interest in the treatment and have refused to continue it.

**Hypertrophy of Pylorus in Adult.**—Barrie and Anderson report the case of a woman, aged 27, with two weeks' history of constant circumumbilical pain intense enough to keep her awake at night and of pain and a feeling of distension between the breasts immediately after taking food. She had vomited after every meal, and this had relieved the pain between the breasts. She had lost weight. Four years previously she had had a similar but less severe attack associated with melena, but the symptoms had lasted a fortnight. Her appetite had been good between these two attacks, but eggs, pastry and bacon caused indigestion. Roentgenoscopy after a barium meal indicated hypertrophy of the prepylorus, for which a partial gastrectomy

was performed. The surgical specimen showed concentric hypertrophy of the muscular coat of the stomach, pylorus and duodenum, with massive eosinophil infiltration of the pylorus and peculiar para-arterial giant cell follicles. The evidence suggests that this is an example of a true organic intestinal allergic reaction. The woman did not tolerate certain foods well; she had constant blood eosinophilia and a localized tissue eosinophilia of the pylorus. There were giant cell follicles in the pylorus which closely resembled follicles found in the heart muscle of patients who have become sensitive to neoarsphenamine.

## Medical Press, London

**220**:485-506 (Dec. 8) 1948

Disorders of Personality. R. B. Sharp.—p. 490.
Exercises and Obstetric Analgesia. Helen E. Rodway.—p. 494.
*Diagnosis and Treatment of Low Backache. M. G. Good.—p. 496.

**Low Backache.**—Good differentiates backache into a symptomatic or secondary and a primary form. The secondary form occurs as a symptom of organic illness in infectious diseases such as smallpox, influenza or typhoid, and in renal or gynecologic disorders. Primary backache may be due to morbid conditions in (1) muscles, ligaments and fascia; (2) joints and bones, and (3) nerves. Experiences in the British Army with several hundred cases seem to justify the conclusion that a myalgia of lumbar, gluteal and other muscles is responsible for most cases of low backache. The main symptom of this form of myalgia is pain of two kinds—a dull, deep kind, which cannot be localized properly and a superficial type which is localized. The pain is aggravated by contraction and relieved by relaxation of the affected muscles. Sometimes it increases during sleep and awakens the patient. The objective signs center around muscular areas termed "myalgic spots" which, as a rule, are harder to the touch than the surrounding parts, but nodules are absent. Pressure on a myalgic spot produces a severe pain. The author discusses the lumbar, gluteal, lumbogluteal and dorsal forms of myalgia. A salt-poor vegetarian diet has a beneficial effect on myalgias and infra-red ray treatment followed by strictly local massage gives satisfactory results provided it is applied to the myalgic areas and not to areas of referred pain. The disadvantages are that massage of myalgic spots is painful and up to several months are often necessary for complete relief. A more rapid and effective relief can be obtained by injection of 1 to 2 cc. of 1 per cent procaine into each myalgic spot. Failure of this local anesthesia is due to a faulty technic; the injections have to be made into accurately located myalgic spots.

## New Zealand Medical Journal, Wellington

**47**:537-604 (Dec.) 1948. **Partial Index**

*Thiouracil versus Surgery: Tentative Comparison based on 100 Treated Cases with Note on Radioactive Iodine. E. J. Fischmann and A. Fischman.—p. 537.
Tuberous Sclerosis with Cerebral Neoplasm: Report of Case Benefited by Operation. J. C. Parr.—p. 550.
Patent Ductus Arteriosus, Review of Results of 20 Surgical Closures, and Description of Intrapericardial Ligation. J. Borrie.—p. 569.
Collapse Therapy in Pulmonary Tuberculosis: Contemporary View. B. C. Thompson.—p. 580.
Manipulation and Treatment of Pain in Chest. J. McM. Mennell.—p. 586.
Poliomyelitis in Pregnancy. C. H. Garlick.—p. 599.

**Thiouracil versus Surgery.**—One hundred patients treated with thiouracil since 1944, 50 of whom ceased medication, were analyzed by Fischmann and Fischman with a view to obtaining data regarding the relative merits of surgery and thiouracil in the treatment of thyrotoxicosis. There is no justification for treating nodular goiter with thiouracil, since the relapse frequency is seven times higher after this than after surgical treatment. Thyroidectomy in nodular goiter permanently abolishes increased thyroid size and also prevents malignancy. In diffuse goiter, surgery and thiouracil have no apparent advantages over one another in regard to applicability, efficiency, unfavorable reactions and the ophthalmopathy of thyrotoxicosis. Treatment with thiouracil is slightly superior with regard to the duration of incapacity and the mortality rate. It does not induce permanent myxedema and avoids the disfigurement caused by the scar. Surgery is superior with regard to reducing thyroid size. It seems that as an alternative to surgery, thiouracil and its allies deserve further trial in the treatment of diffuse toxic goiter. In nodular goiter surgery is the treatment of choice. Radioactive iodine seems by far the most effective of the three available methods of treating toxic goiter. Some authors have called attention to pathologic potentialities involved and have suggested that the therapeutic trial of radioactive isotopes should be limited to cancer.

## Quarterly Journal of Medicine, Oxford

**17**:257-334 (Oct.) 1948

Pulmonary Eosinophilosis. R. Viswanathan.—p. 257.
Review of Antihistamine Drugs. R. B. Hunter and D. M. Dunlop.—p. 271.
*Etiology of Constrictive Pericarditis, with Special Reference to Tuberculous Pericarditis, Together with Note on Polyserositis. G. W. S. Andrews, G. W. Pickering and T. H. Sellors.—p. 291.

**Causation of Constrictive Pericarditis.**—Andrews and his co-workers report 11 cases of chronic constrictive pericarditis in 6 men and 5 women between the ages of 18 and 63. Constrictive pericarditis is a clinical entity which should be differentiated from other forms of adherent pericardium and from polyserositis. Ascites and edema are its chief symptoms; venous congestion and enlarged liver are the chief physical observations. The heart itself exhibits little abnormality. The pericardium is thick and fibrous, and usually reveals no clue as to the nature of the causative disease. Constrictive pericarditis is not due to antecedent acute pericarditis arising from rheumatism, uremia, myocardial infarction or malignant metastasis. During a seven year period all cases of other forms of acute pericarditis—namely, 18 cases of acute tuberculous pericarditis, 7 cases of acute septic pericarditis and 1 case of so-called idiopathic pericarditis—have been studied. In 16 of the 18 patients with acute tuberculous pericarditis, 14 male and 4 female patients between the ages of 4 and 49 years, 4 without and 14 with tuberculosis of other serous cavities (polyserositis), constrictive pericarditis developed. Pericardiectomy was performed in 9 of these patients, of whom 3 died; the remaining 6 improved greatly. The pericardium showed a healed scar in 1 and active tuberculosis in 7 seven months to five and a half years from the onset. Pericardiectomy in the presence of active tuberculosis does not seem to increase the liability to dissemination of the disease. Of 7 patients with acute septic pericarditis, 5 died in the acute phase. In neither of the 2 survivors did constrictive pericarditis develop. In the 1 patient with so-called idiopathic pericarditis constrictive pericarditis did not develop. In Great Britain most cases of constrictive pericarditis are due to antecedent acute tuberculous pericarditis. It is the rule for constrictive pericarditis to develop as tuberculous pericarditis. No other form of acute pericarditis has been observed to heal in this way. None of the 11 patients with chronic constrictive pericarditis gave a history of past acute pericarditis. Of all the forms of acute pericarditis, that due to tuberculosis is the most likely to be overlooked.

## South African Medical Journal, Cape Town

**23**:745-784 (Dec. 11) 1948. **Partial Index**

*Incidence of Postural Proteinuria: Relation to Body Build and Nutritional Status. B. M. Bull and M. P. Jones.—p. 746.
Peripheral Nerve Injuries: Results of Treatment. C. A. R. Schulenburg.—p. 750.
Mussel and Fish Poisoning. C. von Bonde.—p. 760.
Brucella Agglutinins: Their Occurrence in Witwatersrand Milk Supplies and in Serum of Normal Persons. W. Lewin, I. Bersohn and N. Richardson—p. 763.
The Brucella Abortion Ring Test for Fresh Milk. G. C. van Drimmelen.—p. 765.
Medical Emergencies in the New-Born: Their Recognition and Treatment. S. Heymann.—p. 766.
Curare: Report. G. G. Henderson.—p. 770.

**Postural Proteinuria.**—Bull and his associates point out that it has long been known that benign forms of proteinuria exist, and it is almost generally agreed that the commonest of these are the postural proteinurias. In earlier investigations one of the authors had demonstrated that the lordotic posture induces and the kyphotic posture prevents proteinuria. The application of a firm binder to the abdomen prevents the proteinuria ordinarily induced by the lordotic posture. Postural proteinuria is accompanied by an increase in the output of all

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the formed elements in the urine, and clearance studies reveal a fall in effective renal blood flow and glomerular filtration rate and a rise in the filtration fraction. The protein can be found in the urine from both kidneys. There is a delay in the foot to tongue circulation time and a rise in pressure in the inferior vena cava in strict association with the proteinuria. Proteinuria can be induced in subjects with large and easily palpable livers by rotating the liver manually so that its anterior surface moves inferiorly. In this investigation the authors are concerned with the incidence of postural proteinuria and with whether postural proteinuria is more common in certain constitutional types. Three hundred and seven boys and youths between the ages of 6 and 20 years, 123 girls between the ages of 6 and 13 years, 50 medical students between 20 and 30 years of age and 50 male subjects over the age of 50 years were investigated. It was found that the incidence of postural proteinuria rose from approximately 1 : 3 in the 6 to 9 year age group to approximately 3 : 4 in the 14 to 16 year age group and then decreased to about 1 : 10 in older men. There was no correlation between postural proteinuria and the state of nutrition.

## Acta Ophthalmologica, Copenhagen

**26**:395-582 (No. 4) 1948. **Partial Index**

Spectrometric, Photoelectric Determination of Fluorescence of Eye Lens, Quantitative and Objective Method for Experimental Investigations. S. E. Brolin.—p. 395.
Experiences with Iridencleisis Antiglaucomatosa with Remarks on Value of Early Operation in Glaucoma. A. Dellaporta.—p. 413.
Localization of Foreign Bodies in Eye by Bone-Free Radiography. K. Lindblom.—p. 439.
*Lipoma Conjunctivae in Three Generations. J. Sæbø.—p. 447.
Medical and Surgical Treatment of Serpiginous Ulcer of Cornea. R. Friede.—p. 509.
Case of Herpes Zoster Ophthalmicus Complicated with Neuroretinitis. J. Jensen.—p. 551.
*Variations in Size and Shape of Eye. S. Stenström.—p. 559.

**Conjunctival Lipoma in Three Generations.**—Conjunctival tumors such as lipomas are comparatively rare. Sæbø reports 3 patients with such tumors. The patients belonged to three generations of the same family, indicating a hereditary anomaly. The first case concerned a woman, aged 51; a growth was observed in her right eye after birth, but this growth never caused any inconvenience. There was slight bulging of the lateral part of the superior palpebra. About 5 mm. outside the corneoscleral limbus there was a yellowish white vertical conjunctival fold. When the eye was wide open a yellowish white tumor was seen extending backward from the conjunctival fold. Its thickness was about 5 mm., and the consistency soft and elastic. The tumor was firmly adherent to the bulbar conjunctiva, but freely movable against the underlying sclera. The daughter of this woman, aged 22, had a similar congenital growth. According to the mother's information her father had a similar tumor in his right eye. Her father is now dead, but a photograph shows a fold in his right eye, similar to that of the two others.

**Variations in Size and Shape of Eye.**—Stenström points out that for a satisfactory roentgenographic localization of a foreign body in the eye, the first essential is to ascertain whether the foreign body lies within or outside the bulb. In certain cases this can be done only if the size of the bulb is known. In earlier procedure, consideration could not be paid to this matter, as no method was available for measuring the length of the bulb in vivo. Rushton's procedure makes this possible. Stenström, with the aid of Rushton's method, has made longitudinal measurements of a large number of eyes, at the same time measuring the horizontal equatorial diameter according to the method of Berg. The results thus obtained are reported. The author stresses that the size and shape of the eye show such decided variations that an eye of average size cannot be reckoned with when foreign bodies have to be localized in the orbit. Not even if the refraction of the eye is known can one work with a schematic value of the axial length. Where the greatest precision is required, and especially in the borderline cases in which the foreign body lies close to the posterior pole of the eye, one should, if possible, measure the length and equatorial diameter of the eye. If this is impracticable, the great variations in the size of the eye should be taken into account.

## Cardiologia, Basel

**13**:177-240 (No. 4) 1948

*Recognition and Treatment of Threatened Cardiac Infarction. M. Holzmann.—p. 177.
Endocardial Electrocardiogram Under Experimental Pathologic Conditions of Pericardium and of Myocardium. E. Coelho, J. M. Fonseca and Adelaide Constantino.—p. 193.
Paradoxical Behavior of Electrocardiogram with Exercise Tests in Persons with Coronary Insufficiency. Adriana Mussafia.—p. 212.
Continuous Measurement of Arterial Oxygen Saturation in Man; Clinical Oximetry with Swedish Oximeter According to Millikan. Inga Lindgren.—p. 226.

**Threatened Cardiac Infarction.**—Holzmann reports 4 typical cases of acute severe angina pectoris in 3 men between the ages of 38 and 52 and in a woman aged 53. This syndrome is characterized by repeated attacks of angina pectoris with increasing frequency and intensity which first results from exertion, but later may occur while at rest. The duration of the attack may exceed the limit of ten to fifteen minutes and there may be no response to the usual dose of glyceryl trinitrate. In the author's cases the syndrome of acute severe angina pectoris was a prodrome of cardiac infarction. The electrocardiogram of 2 of these patients showed peculiar changes with a lowering of the ST segment which were interpreted as protracted coronary insufficiency, being considered as a prodromal phase of the infarction. In 1 case the attempt was made to prevent the threatened coronary thrombosis by combined treatment with intravenous injections of heparin and dicumarol* orally. An infarction of the posterior wall occurred with mild clinical symptoms, suggesting that the prophylactic treatment was instituted too late. Treatment with heparin and dicumarol* should be instituted immediately in cases of acute severe angina pectoris and should be combined with vasodilators such as aminophylline. In the presence of signs of inflammation additional administration of penicillin is recommended.

## Deutsche medizinische Wochenschrift, Stuttgart

**73**:621-660 (Dec. 17) 1948. **Partial Index**

Pathogenesis of Gastric Ulcer. G. von Bergmann.—p. 621.
Pulmonary Segments in Lobar Pneumonia. C. Esser.—p. 631.
Diagnosis of Hemochromatosis. P. Büchmann and G. Schenz.—p. 634.
Botulism. W. Wasmuth.—p. 636.
Possibilities of Treating Hepatic and Biliary Disturbances with Hormones. G. Venzmer.—p. 638.
*Use of Methyl Thiouracil During Pregnancy and Lactation. W. Bickenbach, M. Hess and A. Loeser.—p. 640.

**Use of Methylthiouracil During Pregnancy and Lactation.**—Bickenbach and his associates found in experiments on rats that when mother animals were given methylthiouracil before mating and during part or even the whole length of gestation the development of the young animals at birth showed no visible changes. However, when methylthiouracil medication of the mother animal was continued during lactation, the nursing young commenced to show signs of cretinism beginning with about the second week of life. The symptoms of cretinism proved to be reversible, for when the young were separated from their mother the signs of cretinism subsided, but the young were extremely susceptible and few survived separation from the mother. Signs of cretinism and high death rate were observed also when the mother animal was given methylthiouracil only during the period of lactation. This indicates that the substance is excreted in the milk of rats. The authors warn that the fact that rats remain unimpaired by methylthiouracil during gestation cannot be applied to human conditions, especially since the placental mechanism in human subjects differs from that in rats.

## Harefuah, Jerusalem-Tel Aviv

**35**:65-80 (Nov. 15) 1948. **Partial Index**

*Oral Administration of Penicillin in Infants. B. Z. Verbin.—p. 65.
BCG Vaccination Against Tuberculosis. A. Zifrony.—p. 68.

**Penicillin by Mouth for Infants with Diarrhea.**—Verbin gave penicillin by mouth to 95 infants with acute diarrhea. Ninety of these recovered and 5 died. The author gained the impression that this method of administration is effective in purely intestinal disturbances as well as in parenteral complications. He was able to prove in experiments that penicillin is

absorbed in therapeutically active amounts after oral administration to infants. Laboratory tests have shown that the acidity of the infantile stomach is lower than that of the adult stomach, the gastric juice of adults exerting a destructive effect on penicillin, whereas in infants this is not the case. The intestinal flora of infants with diarrhea is chiefly gram positive and the administration of penicillin changes it to gram negative.

## Nederlandsch Tijdschrift v. Geneeskunde, Amsterdam

**92**:3705-3812 (Nov. 13) 1948. **Partial Index**

*Constitutional and Emotional Factors in Etiology of Essential Hypertension. J. Groen and J. H. Reisel.—p. 3714.
Urticaria After Emotional Experiences. G. F. Van Balen.—p. 3723.
Artificial Feeding of Healthy Infants. P. J. M. Haanappel.—p. 3726.
*Etiologic Conditions in Pulmonary Cancer. W. F. Wassink.—p. 3732.

**Emotional Factors in Essential Hypertension.**—According to Groen and Reisel it is well known that the blood pressure of normal persons fluctuates considerably under the influence of emotions, and in patients with essential hypertension this seems to be so to an even greater extent. Frequently patients themselves ascribe an intensification of their hypertension to some emotional annoyance. The authors tried to determine whether the character structure of these patients is such that they are predisposed to emotional conflicts and also whether the onset or exacerbation of the hypertension was preceded by an emotional upset. They obtained their data from 50 patients with essential hypertension whose ages varied between 18 and 60 years. They found that these patients are usually active, hard working persons with a tendency to perfectionism. They are inclined to lead and to dominate. They are not satisfied with themselves, and while outwardly they may appear self assured, inwardly they are not. Many make great efforts to adjust themselves to their surroundings; they have a great need to be loved and appreciated. One of the most fundamental characteristics of these patients is a strong destructive aggressiveness, and this combined with the need for love and appreciation makes for chronic conflict situations.

**Pulmonary Cancer.** — Comparing the occupations of 143 patients with cancer of the lung and trachea with the occupations of hundreds of other patients with cancers in which occupation seems to be without significance, Wassink gained the impression of a high incidence of cancer of lung and larynx among brain workers and a low incidence of this type of cancer among agricultural workers. Further investigations suggested that excessive smoking and remaining for long periods in rooms in which the air is laden with tobacco smoke is one of the most important exogenous causal factors in cancer of the lung.

## Nordisk Medicin, Stockholm

**40**:2025-2076 (Nov. 5) 1948. **Partial Index**

*Temperature and Pulse in Acute Appendicitis Illustrated by 2,250 Cases. E. Dahl-Iversen and H. Rahbek Sørensen.—p. 2026.
Spinal Anesthesia: I. Headache Treated with Physiologic Salt Solution Intraspinally. J. C. Skou.—p. 2030.
Anesthesia and Asthma. Preliminary Report. G. Haglund.—p. 2032.
Retropubic Prostatectomy According to Millin. J. Östenfeld.—p. 2038.
*Miliary Tuberculosis Treated with p-Aminosalicylic Acid (PAS) and with p-Aminosalicylic Acid and Streptomycin. B. Carstensen and L. Söderhjelm.—p. 2039.
Chyluria and Hyperlipemia. K. Boman.—p. 2042.
Bilateral Pneumothorax after Thyroidectomy. E. Christensen.—p. 2044.
Treatment of Swelling of Arm After Operation for Cancer of Breast. E. Müllbourn.—p. 2046.
Diagnosis of Omental Adhesions to Anterior Abdominal Wall. K. Stray.—p. 2047.
Dislocation Fracture of Hip Joint. W. Mathisen.—p. 2049.
Cancer Cells in Prostatic Secretions. C. M. Fayers and C. Jönsson.—p. 2051.
Tetanus after Burn Probably Caused by Plastic Operation. G. Asboe Hansen.—p. 2054.

**Temperature and Pulse in Acute Appendicitis Illustrated by 2,250 Cases.**—Dahl-Iversen and Sørensen found agreement between the temperature of children and adults in acute appendicitis. According to their material the clinical value of temperature and pulse rate in acute appendicitis is slight. There is no temperature or pulse rate, they assert, which is characteristic of appendicitis, and differential diagnosis with respect to febrile disorders with similar symptoms must be made along other lines. There is no typical temperature or pulse rate for the different types of appendicitis. Temperature and pulse also are not important in evaluation of the gravity of a case. Normal or slightly elevated values do not exclude a grave case. In cases where appendicitis is suspected the history and especially the abdominal findings should hold the central place in diagnostic consideration. In a given case a rise in temperature and pulse points to aggravation of the pathologic process.

**Miliary Tuberculosis Treated with Para-Aminosalicylic Acid (PAS) and with Para-Aminosalicylic Acid and Streptomycin.** — Carstensen and Söderhjelm say that while both para-aminosalicylic acid and streptomycin possess high tuberculostatic activity, with streptomycin apparently somewhat superior, streptomycin because of its toxic properties has shown itself unsuited for use in prolonged treatment. In experimental tuberculosis in mice better therapeutic results have been attained by combination therapy with para-aminosalicylic acid and streptomycin than with either agent alone. Three cases of typical miliary tuberculosis are published. In the first, with death from meningitis, there was roentgenologic regression of the miliary pulmonary changes in the lungs after six months' treatment with para-aminosalicylic acid, and necropsy revealed healing of miliary foci in lungs, liver, spleen and kidneys. In the next case, with decided changes in lungs and ocular fundus, healing has apparently occurred after combination therapy; para-aminosalicylic acid was given almost constantly for ten months, streptomycin for two periods of twenty-one and eighteen days respectively (total amount, 32.7 Gm. and 18 Gm. respectively). In the third instance the results are promising after combination therapy with para-aminosalicylic acid for three months and streptomycin for eleven days (total amount, 20.4 Gm.). The authors advocate prolonged treatment of recent tuberculous manifestations with para-aminosalicylic acid, in grave conditions supplemented with streptomycin for shorter periods.

## Revue d'Hématologie, Paris

**3**:251-344 (No. 3) 1948. **Partial Index**

Iontophoresis; Its Part in Biologic and Medical Research. E. Wiedemann.—p. 251.
Influence of Incompatibility of ABO System on Rh Antagonism. J. J. Van Loghem Jr. and J. Spaander.—p. 276.
Research and New Theories on Pathogenesis of Erythroblastosis fetalis. A. S. Wiener.—p. 287.
*Macrocytic Anemia Associated with Cirrhosis of Liver (Pathogenesis and Treatment). L. Braier.—p. 293.

**Macrocytic Anemia in Cirrhosis of Liver.**—According to Braier, Laënnec's cirrhosis of the liver is frequently associated with mild macrocytic anemia, which differs from that associated with Biermer's disease because of the absence of megalocytes and of anisopoikilocytosis. It is an "isomacrocytosis" in contrast to the anisomacrocytosis associated with Biermer's disease. The concept according to which macrocytic anemia associated with Laënnec's cirrhosis of the liver may be caused by an insufficient storage of the antianemic factor—i. e., by severe lesions of the hepatic parenchyma—is erroneous. Eppinger's and Naegeli's concepts of hypersplenia may explain certain types of anemia in cirrhotic patients, but in the majority of cases the macrocytic anemia like the cirrhosis itself depends on complex and only partly known disturbances of nutrition and of metabolism. The macrocytic anemia in cirrhosis is often resistant to antianemic agents, such as liver extract, blood transfusions and iron. The author treated 6 patients with large doses of folic acid combined with very large doses of concentrated extract of liver by mouth, and 5 patients with 2 Gm. of synthetic methionine daily by mouth for several weeks and even for several months. Definitely favorable results could not be obtained in any of these cases, not even in those patients whose general clinical condition improved under a dietary regimen devised for the protection of the liver by containing lipotrophic agents and brewer's yeast. Ten patients with Laënnec's cirrhosis, 1 of them with macrocytic anemia, were given 5 Gm. of choline daily by mouth for several weeks; although choline did not exert any disadvantageous effect on the blood picture of the patients, the drug was ineffective in the case of the patient with macrocytic anemia.

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# Book Notices

**The Renal Origin of Hypertension.** By Harry Goldblatt, M.D., C.M., Director, Institute for Medical Research, Cedars of Lebanon Hospital, Los Angeles. Publication Number 14, American Lecture Series. A Monograph in American Lectures in Pathology, edited by Paul R. Cannon, M.D., Professor of Pathology, University of Chicago, Chicago. Fabrikoid. Price, $2.75. Pp. 126, with 38 illustrations. Charles C Thomas, 301-327 E. Lawrence Ave., Springfield, Illinois, 1948.

This monograph constitutes an excellent summary of recent results in the field of experimental renal hypertension and their application to the pathogenesis and treatment of human hypertension. Goldblatt reviews earlier and at best partially successful attempts at producing hypertension experimentally by various procedures applied to the kidney and then describes his classic work in producing chronic and malignant hypertension in dogs and other species by moderate and severe constriction of the renal arteries. He points out that in long-standing chronic experimental renal hypertension there is little arteriosclerosis and arteriolosclerosis but that the pathologic changes found in experimental malignant hypertension resemble those found in malignant hypertension in man. In discussing the pathogenesis of experimental renal hypertension, Goldblatt considers that a neurogenic mechanism is not involved but that the anterior pituitary and the adrenal cortex may possibly be concerned. He then discusses the renin-hypertensinogen-hypertensin-hypertensinase system and indicates that the origin of renin from the renal tubule cells or the cells of the juxtaglomerular apparatus is still unsettled. He suggests that the alteration in renal circulation produced by renal artery constriction may produce experimental renal hypertension through an increased secretion of renin by the kidney. He considers less likely the possibility that pressor amines or other recently demonstrated vasoactive substances produced by the kidney play significant roles in pathogenesis. Goldblatt reviews the largely negative results with various drugs (including thiocyanate), vitamins, hormones and renal extracts in the treatment of experimental renal hypertension and points out that the results in essential hypertension have not been dissimilar. He favors the view that the therapeutic and prophylactic effects of heterologous hog renin in experimental renal hypertension are due to antirenin and in doing so commits several important errors in presenting the work of Wakerlin and associates in this field. He points out that sympathectomy has no significant effect in reducing the blood pressure of renal hypertensive dogs and suggests that when there is an effect in essential hypertension, a neurogenic factor may be involved pathogenetically. On the basis of results obtained with unilateral nephrectomy in experimental renal hypertension, Goldblatt wisely recommends this procedure for human hypertension only when the renal involvement is definitely unilateral. On the basis of admittedly incomplete evidence, he favors the renal origin of essential hypertension. This monograph is definitely recommended to all students and practitioners of medicine who wish to remain abreast of research in a field which should some day bear the fruit of understanding, successful treatment, and even prevention of human hypertension.

**The Frontal Lobes.** Proceedings of the Association December 12 and 13, 1947, New York. Editorial Board: John F. Fulton, M.D., Charles D. Aring, M.D., S. Bernard Wortis, M.D. Research Publications Association for Research in Nervous and Mental Disease, Volume XXVII. Cloth. Price, $12.50. Pp. 901, with 237 illustrations. Williams & Wilkins Co., Mt. Royal & Guilford Aves., Baltimore 2, 1948.

The momentous discovery by Egas Moniz, in 1935, that certain mental disorders could be relieved by surgical operations on the frontal lobes has stimulated an enormous amount of work along various lines. The present volume, containing the papers presented at the meeting of the Association for Research in Nervous and Mental Disease, in December 1947, is at once a record of work done and a signpost toward further researches. The first half is devoted to experimental work of various kinds and the second to clinical experiences, particularly with frontal lobotomy. In his preface, Fulton states: "The tenor of the lobotomy papers is of challenging interest, both in respect of the improvement reported in groups such as schizophrenics, and also in the remarkable results in connection with the relief of intractable pain."

The contributions vary greatly in style and cogency. Some are difficult to follow, although the editors are to be commended for their efforts to clarify. Other papers are almost too brief, and reveal tantalizing glimpses of work well begun, but bristling with unanswered questions. Psychological studies and speculative contributions are rather disappointing. Rylander, of Stockholm, has a fine chapter on personality alterations after lobotomy, although one must suspect that in many of his patients the lobotomy was too extensive, and that more restricted lesions would have led to better clinical results. The mystery as to why lobotomy should relieve the intolerable pain of cancer, tabes dorsalis, phantom limb, and so on is not solved, particularly since it appears that the pain threshold and reaction tests are indicative of even greater sensitivity after lobotomy. Another paradox requiring solution is the production of rage by one observer and its abolition by another, both apparently working on the same area in the frontal lobe in animals. In addition to chapters dealing with psychosurgery, there are also discussions of language disorders, epilepsy, motor and autonomic reactions in relation to the frontal lobes. Now, it appears that those areas of the brain, considered by a former generation to be silent areas, are gradually yielding their secrets to those who know what questions to ask and how to interpret the answers.

**Pharmacology, Therapeutics and Prescription Writing for Students and Practitioners.** By Walter Arthur Bastedo, Ph.G., Ph.M., M.D., Consulting Physician, St. Luke's Hospital, New York. Fifth edition. Cloth. Price, $8.50. Pp. 840, with 82 illustrations. W. B. Saunders Co., West Washington Sq., Philadelphia 5, 1947.

Bastedo's "Pharmacology, Therapeutics and Prescription Writing" is intended for students and practitioners. This book provides information that is of practical importance in the everyday life of a practitioner and student. There are those who insist that the subject of therapy today has become so broad that it is impossible to include in one volume all of the essential information. If there is adequate reason for this attitude, Bastedo's book is one of several that should be in a medical library. If, however, there are some who feel that only one book is necessary, this volume could be considered as one of several choices. The tenet of the author in his writings is obvious in his introduction, which begins "Medicine sometimes cures, it often relieves, it always consoles." He has discussed with discerning clarity treatment measures that are in common use and the actions of drugs that are well known or should be well known.

**Pathologie des Kohlehydratstoffwechsels.** Von Prof. Dr. E. Frank, Direktor der II. medizinischen Klinik der Universität Istanbul. Cloth. Price, 24 Swiss francs. Pp. 342, with 20 illustrations. Benno Schwabe, Klosterberg 27, Basal 10; imported by Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

While the study of the pathology of carbohydrate metabolism is well presented here, the volume is designed for the investigator and student of internal medicine and the preclinical sciences rather than as a practical guide to the clinician. In the opening section, the researches on experimental diabetes are divided into three periods, the Minkowski-Banting era (pancreatic diabetes and insulin), the Houssay-Young-Long era (the roles of the anterior pituitary gland and the adrenal cortex in carbohydrate metabolism) and the alloxan diabetes era. This is followed by sections on types of pituitary diabetes in human pathology, insulin, pathologic anatomy of the pancreas in diabetes mellitus, diabetic coma, hyperinsulinism, the pathology of the renal threshold, and glycogen disease (Von Gierke's disease). An extensive discussion of acidosis is also included. The presentation concludes with a brief discussion of the so-called benign melliturias. The collection and evaluation of the literature on the pathology of carbohydrate metabolism is extensive and has been done with care: the book should be of great value to the pathologist, the physiologist and the biochemist. An extensive bibliography of some 23 pages covers the literature to the period of 1947. It might be mentioned that a legend of the discovery of pancreatic diabetes by Minkowski in 1889, new to this reviewer, is related in the opening chapter. Since Minkowski was the "great and honored teacher" of Dr. Frank, this should be authentic.

# Queries and Minor Notes

THE ANSWERS HERE PUBLISHED HAVE BEEN PREPARED BY COMPETENT AUTHORITIES. THEY DO NOT, HOWEVER, REPRESENT THE OPINIONS OF ANY OFFICIAL BODIES UNLESS SPECIFICALLY STATED IN THE REPLY. ANONYMOUS COMMUNICATIONS AND QUERIES ON POSTAL CARDS WILL NOT BE NOTICED. EVERY LETTER MUST CONTAIN THE WRITER'S NAME AND ADDRESS, BUT THESE WILL BE OMITTED ON REQUEST.

## PERSISTENT LACTATION

*To the Editor:*—**A patient, aged 32, complains of persistent lactation since the birth of her only child seven years ago. This patient is able to express a cubic centimeter or more of milk from either breast at will. The patient did not nurse her baby, but her breasts were pumped several times while in the hospital to relieve engorgement. She has now been divorced three years and denies any sexual stimulation. The patient is a slender, rather nervous person with small, soft, slightly pendulous breasts and erect nipples. Evidences of mastitis or other masses are absent. Pelvic examination reveals a normal uterus and adnexa. Some months ago she was given methyl testosterone in the form of metandren® linguets, 10 mg. daily for two weeks, without any appreciable effect. I have given her four doses of testosterone propionate, 25 mg. by intramuscular injection, without appreciable effect. What treatment will alleviate this condition?**

**Fred S. Taber, M.D., New Brunswick, N. J.**

ANSWER.—The statement, "This patient is able to express a cubic centimeter or more of milk from either breast at will" probably indicates that the patient is doing just that. This is all the stimulation that the breast needs to continue lactating. Have her try leaving the breast absolutely alone and wearing an uplift brassiere. A small pad can be worn under the brassiere to absorb the milk. Lactation probably will stop in two to six months if the breast is not stimulated by manipulation or stripping.

## DETERMINATION OF THE SEX OF OFFSPRING

*To the Editor:*—**Explain the fact that in almost all animal life the sex of offspring is the same as the relatively stronger parent, because of either age, state of health or natural physical strength. In the process of development when is sex established?**

**Johnson Underwood, M.D., Parkville, Mo.**

ANSWER.—In the human being, neither age, state of health nor natural physical strength has anything to do with the determination of sex of the offspring. The sex is determined at the time of fertilization of the ovum by the spermatozoon. It is the spermatozoon which determines the sex and not the ovum. All sperm and ova have 48 chromosomes to begin with. Each sperm cell has 46 regular chromosomes plus an "x" and a "y" chromosome, whereas each ovum contains 46 regular chromosomes, plus two "x" sex chromosomes. When maturation occurs each sperm cell and ovum divides into two cells. Each of the two ovum cells contains 23 regular chromosomes plus an "x" chromosome, but one half of the sperm cells contain 23 regular chromosomes plus an "x" chromosome and the other half of the sperm cells contain 23 plus a "y" chromosome. If a sperm cell containing 23 chromosomes plus "x" fertilizes an ovum, a female will result because in the union of the sperm and ovum there will be 46 regular chromosomes plus an "x" and an "x" chromosome. If, on the other hand, a sperm cell containing 24 chromosomes plus a "y" fertilizes an ovum, a male will result because in the union there will be 46 regular chromosomes plus an "x" and a "y" chromosome. It is purely a matter of chance as far as we know at present whether a sperm with an "x" or a "y" chromosome will fertilize an ovum. This is borne out by the fact that almost universally about 94 females are born to every 100 males in single births.

## ACUTE NEPHRITIS

*To the Editor:*—**A 21 year old white man has had albumin, casts, red cells and white cells in his urine for the last five months. Ankle edema and decreased renal function are also present. I have diagnosed this as nephritis. How long must I keep him from his work? He has worked little during the past five months, as he has been mostly in bed.**

**Simon Cherkasky, M.D., Kaukauna, Wis.**

ANSWER.—If the patient's nephritis is an initial attack and if there is still evidence of progressive inflammation in the form of urinary changes, decreasing renal function or elevation in blood pressure, it would be inadvisable to allow the patient to return to work. If, however, the renal process has become stabilized, there is little to be gained by further bed rest after a period of five months; gradual increase in activity and ultimate return to light work should be permitted. The work should not involve exposure to chilling or infection, if possible.

## DIURETIC ACTION OF ASCORBIC ACID

*To the Editor:*—**A patient with glomerulonephritis had intractable edema until we gave her heavy doses (1 Gm. daily) of vitamin C. What is the explanation.**

**Bernhard A. Fedde, M.D., Brooklyn.**

ANSWER.—W. Evans (*Lancet* **1**:308, 1938) reported some diuretic action of ascorbic acid given orally in patients with cardiac failure under control conditions. However, the effect was considerably less than that of ammonium chloride or the purine drugs. Similar results were reported by C. F. Shaffer (J. A. M. A. **124**:700, 1944): Intravenous ascorbic acid had no diuretic effect. In 15 out of 20 patients given a mixture of 2 cc. of mercurophylline and 500 mg. ascorbic acid intravenously, an increased urinary output of 500 cc. to 2,000 cc. over the control period occurred in the first twenty-four hours. D. W. Chapman and C. F. Shaffer (*Arch. Int. Med.* **79**:449, 1947) published similar results from the intravenous injection of 2 cc. of meralluride sodium solution and 500 mg. ascorbic acid. The mechanism of this modest diuretic effect is not known, since there have not been studies on urinary sodium excretion. Presumably the effect is on the kidney, but the delayed action after oral administration in the absence of any evidence of acidosis suggests a metabolic effect.

## TESTOSTERONE THERAPY

*To the Editor:*—**I have had requests from middle-aged men for injections of testosterone. Will such medication stimulate or cause cancer of the prostate or other organs? What tests can one make to rule out possibility of cancer before injecting testosterone?**

**M.D., Oklahoma.**

ANSWER.—Before starting a male patient on androgenic hormone therapy, it is, of course, imperative that a careful rectal examination of the prostate be performed. Any firm or fixed nodule is suggestive of cancer and contraindicates use of testosterone. A perineal biopsy would be the procedure of choice in confirming the diagnosis. A serum acid phosphatase determination may be of value, and an elevated level is significant of prostatic carcinoma.

One is not likely to find cancer cells in prostatic secretions examined by the ordinary method. Loss of weight, dysuria, back pain and anemia lead to the suspicion of a mitotic process in the prostate of the elderly man.

Testosterone is of value in aiding erections and easing the mental attitude during the male climacteric and is often of value in decreasing nocturia and easing the irritable bladder.

## RADIOTHERAPY IN CANCER OF RECTUM

*To the Editor:*—**What value has high voltage roentgen therapy in treatment of carcinoma of the rectum?**

**M.D., Illinois.**

ANSWER.—Radiotherapy is, in general, not as good as radical operation, either as a cure for carcinoma of the rectum or as an attempt to relieve symptoms. Generally, roentgen treatment is used as a palliative procedure and is given in doses of approximately 1,500 to 2,500 r per field. This is usually supplemented, in favorable cases, by interstitial radium in the form of needles or seeds. Preoperative roentgen treatment is seldom used for a strictly operable case, but it may be used in some of the higher grade lesions, strictly those of questionable operability. Recently there have been reports of the use of contact roentgen therapy for lesions low in the bowel which offer promising results.

## VASODILATORS IN ACUTE CORONARY DISEASE

*To te Editor:*—**Assuming that vasodilator drugs are contraindicated for acute myocardial infarction, why do some reputable cardiologists employ intravenously administered aminophylline during an attack?**

**Thomas E. Burrow, M.D., Carlisle, Ark.**

ANSWER.—Vasodilator drugs are not used as a rule in acute myocardial infarction because their dilating effect on the peripheral arterioles is such that a considerable fall in blood pressure may [illegible]. Such a fall in blood pressure may affect the coronary circulation adversely.

The use of intravenously administered aminophylline during a coronary attack is a controversial question. Even if the drug does increase blood flow to the noninfarcted areas in the heart it is doubtful that blood supply to the infarcted areas is increased enough to make any appreciable difference in the final result. Furthermore, the drug may produce a fall in blood pressure by its dilating action. This may be counterbalanced by an increase in cardiac output, as experiments with aminophylline in congestive heart failure have shown. Thus, the net result of the drug is much in doubt.

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Ernest E. Irons

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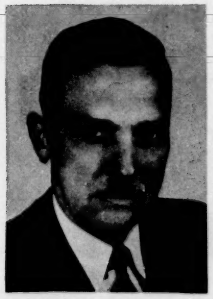

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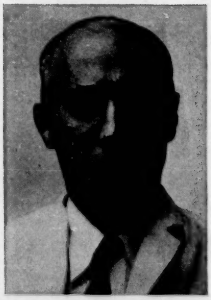

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Chairman
Section on Urology

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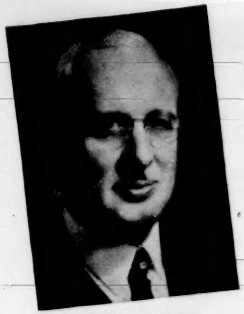

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Newark, N. J.
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Section on Laryngology, Otology and Rhinology

OSCAR A. SANDER
Milwaukee
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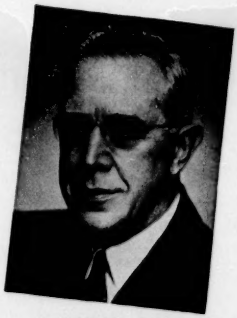
Section on Preventive and Industrial Medicine and Public Health



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HARRY M. WEBER
Rochester, Minn.
Chairman
Section on Radiology

PAUL C. HODGES
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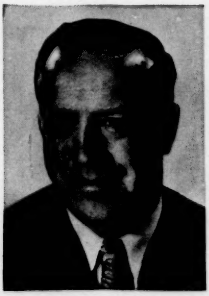
Secretary
Section on Radiology



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Section on General Practice

C. WALTER METZ
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Section on Anesthesiology

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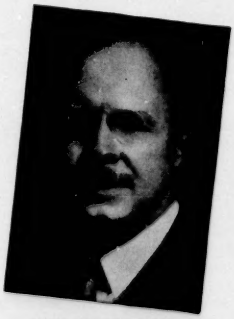
New York
Chairman
Section on Surgery, General and Abdominal

ANTHONY C. CIPOLLARO
New York
Chairman
Section on Dermatology and Syphilology



DAVID M. BOSWORTH
New York
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